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Description

TECHNICAL FIELD

[0001] The present invention relates to an analgesic, diuretic, antitussive, or new preventive or therapeutic drug for ischemic brain disorders, cerebral nerve cell disorders and dementia having for its active ingredient a morphinan derivative or pharmacologically acceptable acid addition salt thereof.

BACKGROUND ART

[0002] Morphine has long been known as a powerful analgesic having a morphinan skeleton, and is widely used even at present. However, this drug has serious side effects that present clinical problems, including drug dependence and respiratory suppression and inhibitory action of smooth muscle movement (constipation). Thus, its use is required to be carefully monitored. There is therefore a need for a powerful analgesic that acts on the central nervous system and that also can be used safely.

[0003] In addition, it has also been reported that drugs that act on opioid receptors effect urination (J.D. Leander, J. Pharmacol. Exp. Ther., 227, 35 (1983)), and thus the effective use of that action is also desired.

[0004] On the other hand, known examples of powerful antitussives that act on the central nervous system include codeine and dextromethorphan. Although these drugs are used not only for medical purposes, but are also widely used as one ingredient of comprehensive cold medications, they too essentially have serious side effects that present clinical problems, including drug dependency, respiratory suppression and inhibitory action of smooth muscle movement (constipation) and psychotomimetics. In particular, in view of the seriousness of the abuse of antitussives containing codeine and the psychotomimetics of dextromethorphan, a powerful yet safe antitussive is desired that acts on the central nervous system.

[0005] Aside from the above, there has been an increase in recent years in various types of ischemic diseases of the cerebrouascular and cardiovascular system accompanying increasing of aged people. Cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis and cerebral phlebothrombosis, cerebrovascular disorders caused by intracerebral hemorrhage and intracerebral thrombus, and functional brain damage caused by head injury and so forth bring about a shortage of glucose and oxygen used as energy sources for nerve cell activity. Due to the resulting necrosis of nerve cells at the ischemic site, various symptoms are manifest as sequela of this necrosis, including cerebrovascular dementia and other disorders. In addition, accompanying the increasing proportion of elderly persons in society resulting from prolongation of the average life span, the problem of such diseases as Alzheimer's disease is becoming a serious problem both medically and socially. In the past, drugs that were developed against these ischemic cerebrovascular disorders and psychoneurotic symptoms accompanying senile dementia consisted primarily of those that mainly increased blood flow to the brain to promote the supply of glucose, oxygen and so forth to the ischemic site. Although these drugs are referred with obscure expressions such as cerebral circulatory improvers, cerebral metabolic activators and cerebral function improvers in terms of their action and mechanism, despite being considered to be effective in improving peripheral symptoms such as volitional disorders, emotional disorders and behavioral abnormalities, their effects are not clear with respect to improvement of the core symptoms of dementia such as memory disorders. Thus, at present, since there is no drug which is able to effectively treat these diseases, the development of a therapeutic drug is desired that demonstrates more reliable action and effects while also being safe and easy to use.

[0006] As relevant prior art to the present invention are the following documents which disclose related compounds: EP-A-0374919 (analgesics), J. Med. Chem., 29 (8), 1986, pp. 1551-1553 (opioid agonists) and EP-A-0577847.

DISCLOSURE OF THE INVENTION

[0007] The existence of opioid receptors has been clearly established as receptors involved in analgesic action on the central nervous system. Moreover, these receptors are known to be able to be classified into the three types μ, δ and κ. In addition, σ receptors are also known to demonstrate psychotomimetics. Those agonists having affinity for κ-receptors or δ-receptors have been shown to have strong analgesic activity, while not demonstrating serious side effects that present clinical problems such as drug dependence, respiratory suppression and inhibitory action of smooth muscle movement, that are observed in the case of morphine and so forth, which are μ-receptor agonists. In addition, the psychotomimetics observed in existing κ-receptor agonists is reported to be caused by affinity to σ receptors. Moreover, κ-receptor agonists do not demonstrate cross tolerance with μ-receptor agonists such as morphine. Analgesics free of such side effects have a high degree of usefulness since they can be applied in not only the control of pain in patients having post-operative pain and cancer patients, but can also be widely applied for general pain. In addition, the absence of cross tolerance indicates that these analgesics are effective even in patients that have developed tolerance to analgesics such as morphine. Namely, the object of the present invention is to provide a κ-receptor agonist or δ-

receptor agonist that has powerful analgesic action while not having serious side effects like those of morphine, not having cross tolerance with morphine and so forth, and not demonstrating any affinity whatsoever for σ receptors.

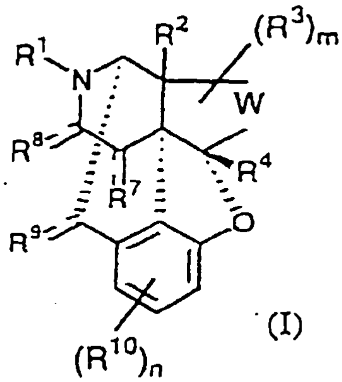
[0008] In addition, a second object of the present invention is to provide a useful diuretic that takes advantage of the effects of opioid action drugs on urination.

[0009] On the other hand, although antitussives such as morphine and codeine, which act on μ receptors, and dextromethorphan, which acts on σ receptors, have been long known, it has not been possible to avoid serious side effects such as drug dependency, respiratory suppression, inhibitory action of smooth muscle movement (constipation) and psychotomimetics. However, those agonists that have affinity for κ receptors have been shown not to demonstrate serious side effects that present clinical problems, such as drug dependency, respiratory suppression, inhibitory action of smooth muscle movement and so forth observed in morphine and so forth, which are μ-receptor agonists. In addition, the psychotomimetics observed in existing κ-receptor agonists is reported to be caused by affinity to σ receptors. Namely, a third object of the present invention is to provide a κ-receptor agonist having powerful antitussive activity that is free of the serious side effects observed in μ-receptor agonists and σ-receptor agonists.

[0010] Moreover, aside from the above, a fourth object of the present invention is to provide a new preventive and therapeutic drug for ischemic brain disorders, cerebroneuronal disorders and dementia.

[0011] As a result of earnest studies to solve the above-mentioned problems, the inventors of the present invention found that the morphinan derivative indicated with general formula (I) is a compound that demonstrates analgesic action, diuretic action, antitussive action and new preventive or therapeutic effects against ischemic brain disorders, cerebroneuronal disorders and dementia while also having the excellent characteristics described above, thus leading to completion of the present invention.

[0012] Namely, the present invention relates to a morphinan derivative represented with general formula (I) below or pharmacologically acceptable acid salt thereof, its production process, as well as its pharmaceutical applications:



(I)

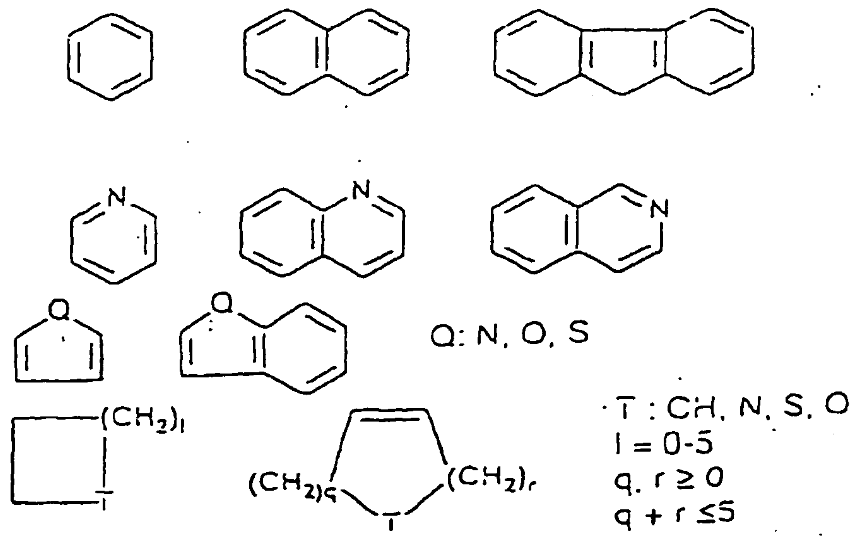
[wherein, ····· represents a single or double bond;

R^1 represents a C_{1-5} alkyl group, a C_{4-7} cycloalkylalkyl group, a C_{5-7} cycloalkenylalkyl group, a C_{6-12} aryl group, a C_{7-13} aralkyl group, a C_{4-7} alkenyl group, an allyl group, a furan-2-yl-C_{1-5} alkyl group or a thiophen-2-yl-C_{1-5} alkyl group;

R^2 represents a hydrogen atom, a hydroxy group, a C_{1-5} alkoxy group, or an alkanoyloxy group having up to 5 carbon atoms;

R^3 represents -A-B-R^{11} [wherein A is -N(R^{12})C(=Y)-, -N(R^{12})C(=Y)Z-, -N(R^{12})- or -N(R^{12})SO_2- (wherein Y and Z each independently represent N(R^{12}), S or O, R^{12} represents a hydrogen atom, a straight chain or branched chain C_{1-5} alkyl group or a C_{6-12} aryl group), B represents a valence bond, a straight chain or branched chain C_{1-14} alkylene group [which may be substituted with at least one type of substituent group selected from a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein from 1 to 3 methylene group(s) may be replaced with carbonyl group(s)], a straight chain or branched chain acyclic unsaturated C_{2-14} hydrocarbon and including 1 to 3 double bond(s) and/or triple bond(s) [which may be substituted with

at least one type of substituent group selected from a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein 1 to 3 methylene group(s) may be replaced with carbonyl group(s)], or a straight chain or branched chain saturated or unsaturated C_{1-14} hydrocarbon group containing from 1 to 5 of at least one type of bond selected from a thioether bond, ether bond and amino bond [wherein no hetero atom is bonded directly to A, and 1 to 3 methylene group(s) may be replaced with carbonyl group(s)]; and R^{11} represents a hydrogen atom, a nitro group, fluorine, chlorine, bromine, iodine or an organic group having the basic skeleton group A shown below:



(which may be substituted with at least one type of substituent group selected from a C_{1-5} alkyl group, a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, an isothiocyanato group, a trifluoromethyl group, a trifluoromethoxy group and a methylenedioxy group);

m is an integer from 1 to 10, which may be selected as desired within the range of the number of hydrogen atoms that can bond with carbon chain W, and each R^3 may be identical with or different from each other R^3 in the case of m being equal to 2 or more;

R^4 represents -A-B-R^{11} (wherein A, B and R^{11} are as defined above), with the proviso that A may alternatively be a valence bond;

R^7 represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine, an oxime group, a C_{1-5} alkyl group (which may be substituted with a hydroxy group), an alkanoyl group having up to 5 carbon atom or a carbonyl group;

R^8 represents a hydrogen atom, a C_{1-5} alkyl group, a cyano group, -COOH, an alkylamido group having up to 5 carbon atoms or a carbonyl group;

R^9 represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine or a carbonyl group;

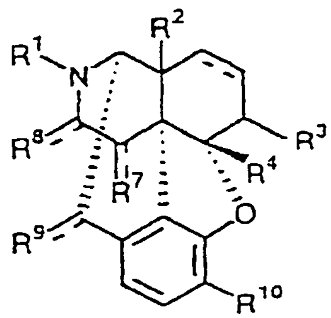
R^{10} represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine, $-SO_3H$, $-OSO_3H$, a nitro group, an amino group, a C_{1-5} alkyl group, an alkanoyl group having up to 5 carbon atoms, an alkanoyloxy group having up to 5 carbon atoms or a C_{1-5} alkoxy group;

n represents an integer from 1 to 3;

W represents a C_{2-5} alkylene group or an unsaturated C_{2-5} hydrocarbon group;

and, the general formula (I) includes the (+) form, (-) form and (±) form];

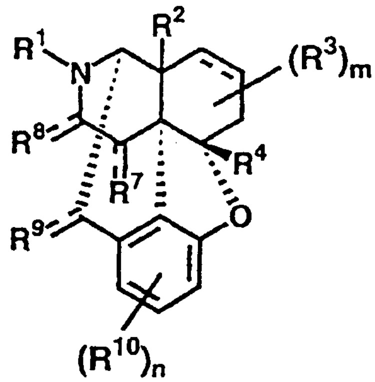
with the proviso that when the compound is represented by the general formula (I-E):



(I-E)

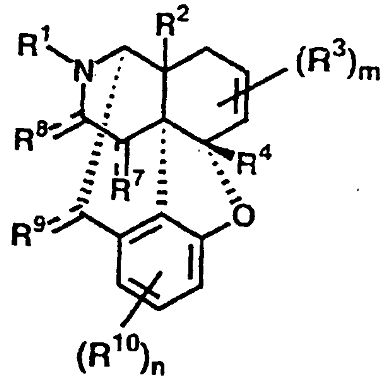
(wherein, $\underline{\cdots}$ represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9 and R^{10} are as defined above, and the general formula (I-E) includes the (+) form, (-) form and (±) form)), at least one of R^7, R^8 and R^9 is a substituent group other than a hydrogen atom.

[0013] Among the above-mentioned preferable compounds, (1) morphinan derivatives or their pharmacologically acceptable acid addition salts represented with general formula (I-A):



(I-A)

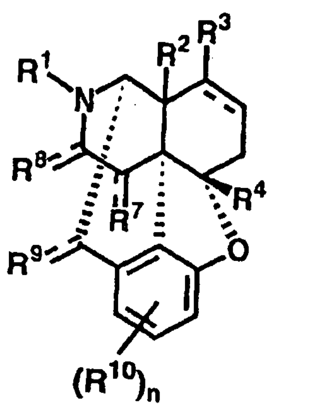
[wherein $\underline{\cdots}$ represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, m and n are the same as previously defined, and the general formula (I-A) includes the (+) form, (-) form and (±) form]; (2) morphinan derivatives or their pharmacologically acceptable acid addition salts wherein W is an alkylene group having 2 or 4-5 carbon atoms or an unsaturated hydrocarbon group having 2 or 4-5 carbon atoms in the general formula (I); and, (3) morphinan derivatives or their pharmacologically acceptable acid addition salts represented with general formula (I-F):



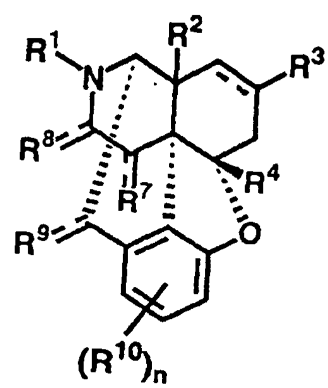
(I-F)

(wherein, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, m and n are the same as previously defined, and the general formula (I-F) includes the (+) form, (-) form and (±) form) are preferable.

[0014] Examples of the morphinan derivatives listed in (1) through (3) in the case of (1) include: a. morphinan derivatives wherein m is an integer from 2 to 6 in general formula (I-A); b. morphinan derivatives represented with general formula (I-G) or (I-H):

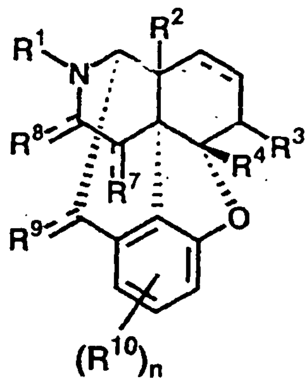


(I-G)



(I-H)

(wherein, • • • represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10} and n are the same as previously defined, and the general formula (I-G) and (I-H) include the (+) form, (-) form and (±) form); and c. morphinan derivatives represented with general formula (I-J):



(I-J)

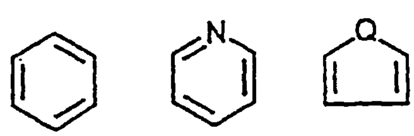
[wherein, $\cdots$ represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10} and n are the same as previously defined and the general formula (I-J) includes the (+) form, (-) form and (±) form].

[0015] Here, preferable examples of R^1 include an alkyl group having 1-5 carbon atoms, a cycloalkylmethyl group having 4-7 carbon atoms, a cycloalkenylmethyl group having 5-7 carbon atoms, a phenylalkyl group having 7-13 carbon atoms, an alkenyl group having 4-7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1-5 carbon atoms, and a thiophen-2-yl-alkyl group having 1-5 carbon atoms, while particularly preferable examples include methyl, ethyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopentenylmethyl, cyclohexenylmethyl, benzyl, phenetyl, trans-2-butenyl, 2-methyl-2-butenyl, allyl, furan-2-yl-methyl and thiophen-2-yl-methyl groups.

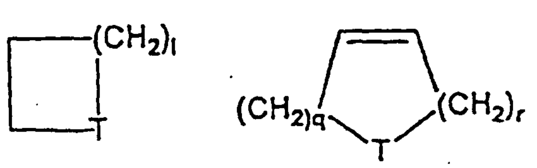
[0016] Among the -A-B-R^{11} groups represented by R^3, preferable examples of A include -$NR^{12}C(=O)$-, -$NR^{12}C(=S)$-, -$NR^{12}C(=O)O$-, -$NR^{12}C(=O)NR^{12}$-, -$NR^{12}C(=S)NR^{12}$-, -$NR^{12}C(=O)S$-, -NR^{12}-, and -$NR^{12}SO_2$-, while particularly preferable exámples include -$NR^{12}C(=O)$-, -$NR^{12}C(=S)$-, -$NR^{12}C(=O)O$-, -$NR^{12}C(=O)NR^{12}$-, -$NR^{12}C(=S)NR^{12}$- and -$NR^{12}SO_2$-. Preferable examples of R^{12} include a hydrogen atom, a straight chain or branched chain alkyl group having 1-5 carbon atoms and a phenyl group, while particularly preferable examples include straight chain or branched chain alkyl groups having 1-5 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and isobutyl groups.

[0017] Among the -A-B-R^{11} groups represented by R^3, preferable examples of B include -$(CH_2)p$- (p=0-6), -$(CH_2)p$-$C(=O)$- (p=1-4), -$CH=CH$-$(CH_2)p$- (p=0-4), -$C\equiv C$-$(CH_2)p$- (p=0-4), -CH_2-O-, -CH_2-S-, -CH_2-O-$(CH_2)_2$-O-$(CH_2)_2$-, -CH_2-O-CH_2-NH-CH_2-O-CH_2-, and -CH_2-O-CH_2-S-CH_2-O-CH_2-, while particularly preferable examples include -$(CH_2)p$- (p=0-6), -$CH=CH$-$(CH_2)p$- (p=0-4), -$C\equiv C$-$(CH_2)p$- (p=0-4), -CH_2-O- and -CH_2-S-.

[0018] Among the -A-B-R^{11} groups represented by R^3, preferable examples of R^{11} include a hydrogen atom or organic groups having the basic skeletons shown below:



Q: N, O, S



T : CH, N, S, O
l = 0-5
q, r ≥ 0
q + r ≤ 5

(which may be substituted with at least one type of substituent group selected from the group consisting of an alkyl group having 1-5 carbon atoms, an alkoxy group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon

atoms, a hydroxy group, fluorine, chlorine, bromine, an amino group, a nitro group, a cyano group, an isothiocyanato group, a trifluoromethyl group, and a trifluoromethoxy group), while particularly preferable examples include a hydrogen atom, phenyl, 3,4-dichlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-difluorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2-fluorophenyl, 4-bromophenyl, 3-bromophenyl, 2-bromophenyl, 4-nitrophenyl, 3-nitrophenyl, 2-nitrophenyl 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-methylphenyl, 3-methylphenyl, 2-methylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 3-furyl, 2-methyl-3-furyl, 4-methyl-3-furyl, 5-methyl-3-furyl, 2-bromo-3-furyl, 4-bromo-3-furyl, 5-bromo-3-furyl, 2-chloro-3-furyl, 4-chloro-3-furyl, 5-chloro-3-furyl, 2-furyl, 3-methyl-2-furyl, 4-methyl-2-furyl, 5-methyl-2-furyl, 3-bromo-2-furyl, 4-bromo-2-furyl, 5-bromo-2-furyl, 3-chloro-2-furyl, 4-chloro-2-furyl, 5-chloro-2-furyl, 3-thienyl, 2-methyl-3-thienyl, 4-methyl-3-thienyl, 5-methyl-3-thienyl, 2-bromo-3-thienyl, 4-bromo-3-thienyl, 5-bromo-3-thienyl, 2-chloro-3-thienyl, 4-chloro-3-thienyl, 5-chloro-3-thienyl, 2-thienyl, 3-methyl-2-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 3-bromo-2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 3-chloro-2-thienyl, 4-chloro-2-thienyl, 5-chloro-2-thienyl, cyclopentyl, cyclohexyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl and 4-trifluoromethoxyphenyl groups.

[0019] In addition, preferable examples of R^2 include a hydrogen atom, hydroxy, acetoxy and methoxy, while particularly preferable examples include a hydrogen atom, hydroxy, acetoxy and methoxy. In addition, preferable examples of R^4 include a hydrogen atom, methyl, ethyl, propyl, acetyl, propioyl and benzoyl groups, while particularly preferable examples include a hydrogen atom, methyl, acetyl and benzoyl groups. Moreover, m is preferably 1 or 2.

[0020] Preferable examples of R^7 include a hydrogen atom, a hydroxy group, chlorine, bromine, an alkyl group having 1-5 carbon atoms, an alkanoyl group having 1-5 carbon atoms and a carbonyl group, while particularly preferable examples a hydrogen atom, hydroxy, acetyl and carbonyl groups.

[0021] Preferable examples of R^8 include a hydrogen atom, an alkyl group having 1-5 carbon atoms and a cyano group, while particularly preferable examples include a hydrogen atom and a cyano group, with a hydrogen atom being especially preferable.

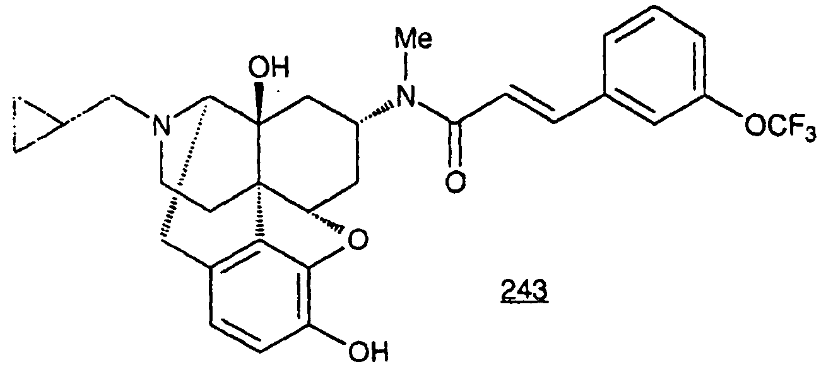
[0022] Preferable examples of R^9 include a hydrogen atom, a hydroxy group, chlorine, bromine and a carbonyl group, while particularly preferable examples include a hydrogen atom and a carbonyl group, with a hydrogen atom being especially preferable.

[0023] Preferable examples of R^{10} include a hydrogen atom, a hydroxy group, chlorine, bromine, a nitro group, an alkyl group having 1-5 carbon atoms, an alkanoyl group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon atoms, and an alkoxy group having 1-5 carbon atoms, while particularly preferable examples include a hydrogen atom, hydroxy, chlorine, bromine, nitro, methyl, ethyl, propyl, acetyl, propioyl, acetoxy and methoxy groups, with a hydrogen atom, hydroxy, acetoxy and methoxy groups being especially preferable. In addition, n is preferably 1 or 2.

[0024] Preferable examples of W include an alkylene group having 2-5 carbon atoms, and an unsaturated hydrocarbon group having 3-4 carbon atoms, while particularly preferable examples include $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $CH{=}CH{-}CH_2$, $CH{=}CH{-}CH_2CH_2$ and $CH_2CH{=}CHCH_2$. However, preferable examples are not limited to these groups.

[0025] Examples of pharmacologically acceptable acid addition salts include inorganic acid salts such as hydrochloride, sulfate, nitrate, hydrobromide, hydroiodide and phosphate; organic carboxylates such as acetate, lactate, citrate, oxalate, glutarate malate, tartrate, fumarate, mandelate, maleate, benzoate and phthalate; and, organic sulfonates such as methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and camphasulfonate. Although hydrochloride, hydrobromide, phosphate, tartrate, and methanesulfonate and so forth are particularly preferable, pharmacologically acceptable acid salts are naturally not limited to these.

[0026] Compound 243 included in the compounds of general formula (I) of the present invention, wherein the line parallel to the solid line and broken line is a single bond, W is $(CH_2)_3$, R^1 is a cyclopropylmethyl group, R^2 and R^{10} are hydroxy groups, R^3 is $-A-B-R^{11}$ wherein A is α-$NR^{12}C(=O)$-, R^{12} is a methyl group, B is -CH=CH- and R^{11} is a 3-trifluoromethoxy group, m and n are both 1 and R^4 is a hydrogen atom (provided that binding position of R^3 and R^{10} is as shown in the following structural formula),



243

is named 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethoxy cinnamamido morphinan.

[0027] In accordance with the above nomenclature system, concrete examples of the compound of the present invention are as follows:

[0028] 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-trifluoromethyl cinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-tritluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-methylcinnamnamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(3-methylphenyl)propiolamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-trifluoromethyl cinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-

trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(3-methyl-phenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethyl cinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyltrans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N- methyl-3-trifluoromethylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5a-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido) morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-

[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido) morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethyl cinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 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7β-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 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17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-methylcinnamamido)morphinan, 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17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-trifluoromethylcinnanamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-methylcinnamamido)-morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-(N-methyl-3-methylcinnamamido)-morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiola-

mido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(4-trifluoromethylphenyl)-propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(3-methylphenyl)-propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido] morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-(N-methyl-3-methylcinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 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17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 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dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(3- furyl)acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan, 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mido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethylcinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(3-furan)-acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-trans-3-(3-furan)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 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17-allyl-4,5α-epoxy-3,14β-dihydroxy-8β-[N-methyl-3-(3,4-dimethylphenyl)propiol-amido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-8β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-8β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihy-

droxy-1-nitro-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-allyl-4,5a-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 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17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 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mido)morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan, 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17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-3-(3,4-dimethyiphenyl)propiolamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethyiphenyl)propiolamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]-morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethyiphenyl)-propiolamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]-morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl- 3-(3,4-dimethyiphenyl)propiolamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan, 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thienyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acryl amido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 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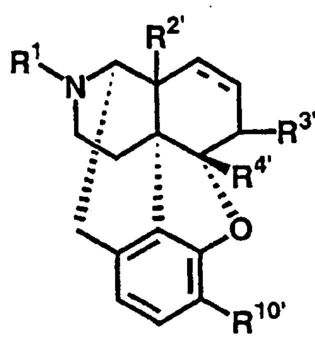
17-methyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-allyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-methyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyltrans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-allyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 17-methyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3- (4-bromo-2-thienyl)acrylamido]morphinan, 17-phenethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido)morphinan, 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-nor-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy3,14β-dihydroxy-7β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-allyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-methyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, 8-homo-17-phenethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-trans-3-(4-bromo-2-thienyl)acrylamido]morphinan, but the present invention is not limited to these compounds.

[0029] Furthermore, the compound of the present invention includes the (+) form, (-) form and (±) form.

[0030] The compound of general formula (I-B):



(I-B)

(wherein ... represents a double bond or single bond;

$R^{2'}$ represents a hydrogen atom, a hydroxy group, an alkanoyloxy group having 1 - 5 carbon atoms, and an alkoxy group having 1 - 5 carbon atoms;

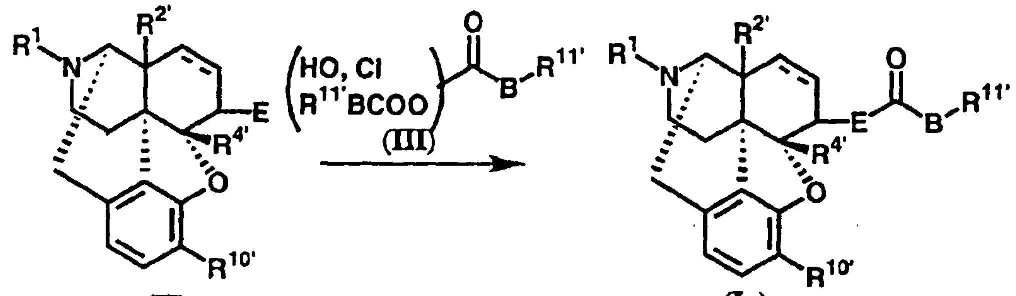
$R^{3'}$ represents -A'-B-$R^{11'}$ (where, A' represents -N(R^{12})C(=Y)-, N(R^{12})C(=Y)Z-, -N(R^{12})- or -N(R^{12})SO_2- (where, Y, Z and R^{12} are the same as previously defined, and wherein R^{12} may be identical or different), $R^{11'}$ is a hydrogen atom or the basic skeleton group A, and B is the same as previously defined);

$R^{4'}$ represents a hydrogen atom, a straight chain or branched chain alkyl group having 1 - 5 carbon atoms, or an alkanoyl group having 1 - 5 carbon atoms;

$R^{10'}$ represents a hydrogen atom, a hydroxy group, an alkanoyloxy group having 1 - 5 carbon atoms, or an alkoxy group having 1 - 5 carbon atoms; and the general formula (I-B) includes the (+) form, (-) form and (±) form), and related modes of the present invention, can specifically be obtained by the following procedure.

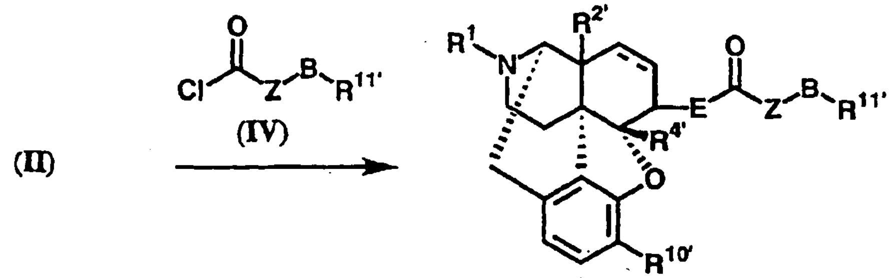
[0031] The compound indicated with general formula (I-B), which is a related mode of the present invention, wherein A' is -N(R^{12})C(=Y)-, -N(R^{12})C(=Y)Z-, or -N(R^{12})SO_2- (where Y represents O or S, and Z represents O, NH or S, and R^{12} is the same as previously defined), can specifically be obtained with the following procedure.

[0032] In general, as shown in Chart 1, said compound can be obtained by condensing the carboxylic acid derivative represented with general formula (III) (wherein B and $R^{11'}$ are the same as previously defined), the formic acid derivative represented with general formula (IV) (wherein Z, B and $R^{11'}$ are the same as previously defined), the isocyanic acid or isothiocyanic acid derivative represented with general formula (V) (wherein B and $R^{11'}$ are the sane as previously defined), or the sulfonic acid derivative represented with general formula (VI) (wherein B and $R^{11'}$ are the same as previously defined) and so forth with the 6-amino form represented with general formula (II) (wherein R^1, $R^{2'}$ $R^{4'}$ and $R^{10'}$ are the same as previously defined, and E represents NHR^{12} (wherein R^{12} is the same as previously defined).



(II)

(Ia)



(Ib)

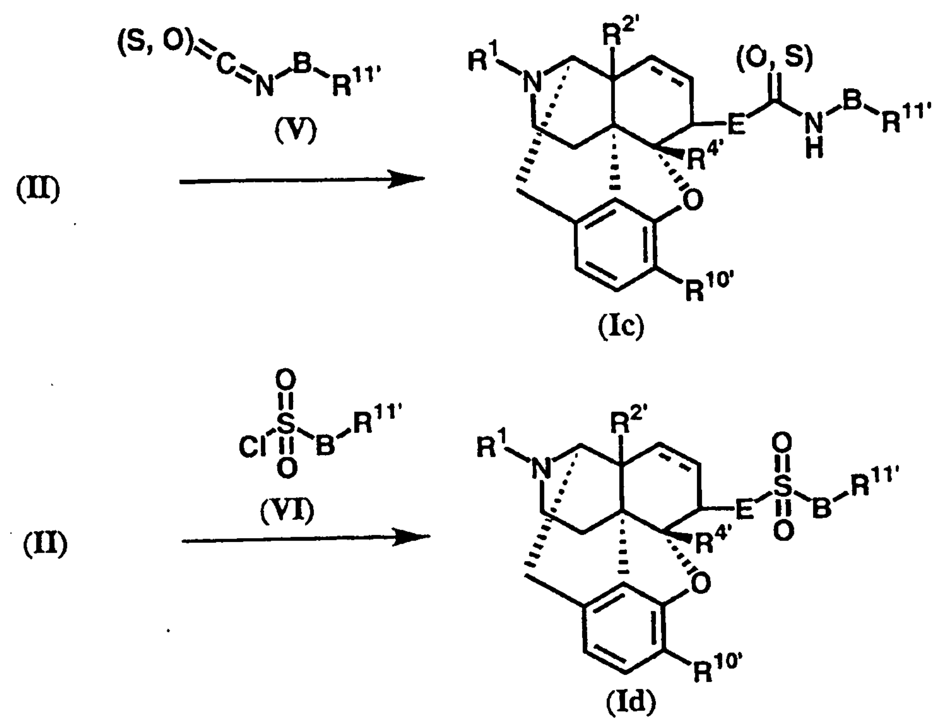


Chart 1

[0033] The 6-amino form used in this condensation can specifically be obtained by the following process.

[0034] As shown in Chart 2, the 6α-amino form represented with general formula (IIaα1) (wherein R^1, $R^{2'}$, $R^{4'}$, and $R^{10'}$ are the same as previously defined, and $R^{12'}$ represents a straight chain or branched chain alkyl group having 1-5 carbon atoms or an aryl group having 6-12 carbon atoms) is obtained by mixing in solvent the 6-keto form represented with general formula (VIIa) (wherein R^1, $R^{2'}$, $R^{4'}$, and $R^{10'}$ are the same as previously defined) and the primary amine represented with general formula (VIII) (wherein $R^{12'}$ is the same as previously defined) followed either by the addition of a suitable amount of acid and hydrogenation in the presence of a metal catalyst, or reduction with a metal hydride reducing agent in the presence of acid. The hydrogenation reaction is preferable for obtaining the α-amino form with high selectivity. However, although the ratio varies according to the simultaneously in the case of reduction by metal hydride reducing agent, and is preferable in that a compound having the desired stereochemistry can be obtained by using ordinary separation and purification methods. In addition, this is also useful as a process for obtaining the amino form with a substrate having functional groups such as olefins and so forth that end up reacting under conditions of hydrogenation. In the case of reduction by a hydrogenation reaction, 1-30 equivalents, and preferably 1-10 equivalents, of amine is used. Although any solvent can be used for the solvent provided it is inactive under conditions of hydrogenation, examples of which include alcohol solvents such as methanol and ethanol, ether solvents such as THF, ether, DME and dioxane, and aromatic hydrocarbon solvents such as benzene and toluene, alcohol solvents are used preferably and methanol is used particularly preferably. Although any acid can be used for the acid provided that it normally forms a salt with an amine, examples of which include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, and organic acids such as benzoic acid, acetic acid and oxalic acid, hydrochloric acid, sulfuric acid and methanesulfonic acid are used preferably. Satisfactory results are usually obtained by using hydrochloric acid in an amount that is 1 equivalent less than the total amount of base. These acids can be added to the reaction system by first converting the substrate and reaction agents into salts. Although all metal catalysts can be used that are normally used in hydrogenation reactions, examples of which include platinum catalysts such as platinum oxide and platinum hydroxide, palladium catalysts such as palladium hydroxide and palladium-carbon, and nickel catalysts such as Raney nickel, a platinum catalyst, and

particularly platinum oxide, is used preferably. Although the reaction can be carried out at a reaction temperature from -30°C to 80°C, and preferably from -10°C to 50°C, and hydrogen pressure from 1 to 100 atmospheres, and preferably from 1 to 30 atmospheres, favorable results are usually obtained at room temperature and normal pressure.

[0035] When reducing with a metal hydride, the amount of amine used is from 1 to 30 equivalents, and preferably from 1 to 15 equivalents. Although examples of solvents used include alcohol solvents such as methanol and ethanol, ether solvents such as THF, ether, DME and dioxane, and aromatic hydrocarbon solvents such as benzene and toluene, alcohol solvents are used preferably, while methanol is used particularly preferably. Although any acid can be used for the acid present in the reaction provided it normally forms a salt with amines, examples of which include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, and organic acids such as benzoic acid, acetic acid and oxalic acid, hydrochloric acid, sulfuric acid, methanesulfonic acid and so forth are used preferably. In addition, these acids can be added to the reaction system by first converting the substrate and reaction agents into salts. Metal hydride reducing agents that can be used to carry out the reaction are those which are relatively stable under conditions in which acid is present, examples of which include sodium borohydride, sodium cyanoborohydride, zinc borohydride, sodium triacetoxyborohydride, tetramethylammonium triacetoxyborohydride and borane-pyridine, with sodium cyanoborohydride being used particularly preferably. Although the reaction can be carried out at a reaction temperature from -30°C to 100°C, and preferably from -10°C to 50°C, satisfactory results are usually obtained at room temperature.

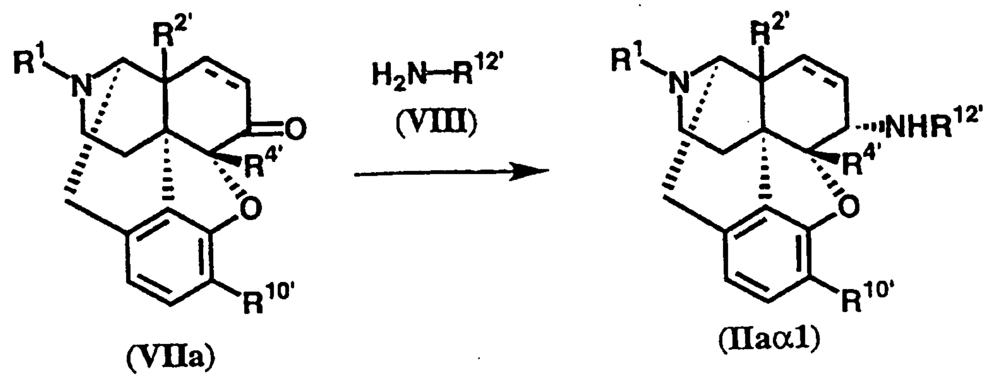


Chart 2

[0036] As shown in Chart 3, the 6β-amino form represented with general formula (IIaβ2) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{10'}$ and $R^{12'}$ are the same as previously defined) can be obtained from the 6-keto form represented with general formula (VIIb) (wherein R^1, $R^{2'}$, $R^{4'}$, and $R^{10'}$ are the same as previously defined) with the three steps described below.

[0037] In the first step, the ketone form is reacted with a secondary amine form having at least one benzyl substituent group represented with general formula (IX) (wherein $R^{12'}$ is the same as previously defined) in the presence of acid to obtain the iminium intermediate represented with general formula (X) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{10'}$ and $R^{12'}$ are the same as previously defined). It is desirable that the reaction be allowed to proceed while removing the water formed either by azeotropic distillation or using a dehydrating agent. 1-30 equivalents, and preferably 1-10 equivalents, of the secondary amine are used. Although any acid can be used for the acid present in the reaction provided it normally forms a salt with amines, examples of which include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, and organic acids such as benzoic acid, acetic acid and oxalic acid, hydrochloric acid, sulfuric acid, methanesulfonic acid and benzoic acid are used preferably, while hydrochloric acid and benzoic acid are used particularly preferably. Processes are preferably carried out wherein these acids are added to the reaction system are first converting the substrate and reaction agents into salts. Moreover, in the case of carrying out the reaction in the presence of weak acid, preferable results may be obtained by adding strong acid to the reaction system as an acid catalyst, examples of which include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, and sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid, with p-toluenesulfonic acid and so forth being particularly preferable. Examples of reaction solvents that can be used include ether solvents such as THF, ether, DME and dioxane, halogen solvents such as dichloromethane and chloroform, aromatic hydrocarbon solvents such as benzene, toluene and xylene, ester solvents such as ethyl acetate and methyl acetate, as well as mixed solvents of these. When using an ordi-

nary Dean-Stark water separator for the purpose of removing water, solvents having excellent azeotropic efficiency and water separation efficiency, examples of which include aromatic hydrocarbon solvents such as benzene and toluene, are used preferably. At this time, the mixing in of an amount of a solvent such as ethyl acetate or THF to an extent which does not decrease water separation efficiency for the purpose of lowering the azeotropic temperature may yield more favorable results.

[0038] Although the reaction temperature is considered to be from 40°C to 200°C, and preferably from 50°C to 150°C, satisfactory results are obtained from 50°C to 130°C. In addition, it has also been a found that a new process is effective wherein water is continuously removed by filling a continuous Soxhlet extractor with a dehydrating agent. Although any of the solvents mentioned above can be used for the solvent in this case, ether solvents, ester solvents and aromatic hydrocarbon solvents are used preferably, while THF, DME, ethyl acetate, benzene and toluene are used particularly preferably. Although examples of dehydrating agents include molecular sieves as well as inorganic dehydrating agents such as anhydrous calcium sulfate, anhydrous copper sulfate, anhydrous sodium sulfate, anhydrous magnesium sulfate and calcium chloride, molecular sieves are used particularly preferably. The amount used is from 1 to 100 times, and preferably from 1 to 30 times as converted from their water retention and the theoretical amount of water formed. Although the reaction temperature is considered to be from 40°C to 200°C, and preferably from 50°C to 150°C, satisfactory results are obtained from 50°C to 120°C. In addition, the reaction can also be carried out by directly adding the dehydrating agent to the reaction system. Examples of dehydrating agents include molecular sieves, inorganic dehydrating agents such as anhydrous calcium sulfate, anhydrous copper sulfate, anhydrous sodium sulfate, anhydrous magnesium sulfate and calcium chloride, and titanic compounds having dehydrating properties such as tetraisopropoxy titanium and titanium tetrachloride. In this case as well, the amount used is from 1 to 100 times, and preferably from 1 to 30 times as converted from their water retention and theoretical amount of water formed. Although the reaction temperature is considered to be from -80°C to 100°C, satisfactory results are obtained from -30°C to 50°C.

[0039] In the second step, the product of the first step is converted to the 6-N-alkyl-N-benzylamino form represented with general formula (XI) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{10'}$ and $R^{12'}$ are the same as previously defined) by reducing with a metal hydride reducing agent without isolating the iminium salt. Although the solvent used in the first step may continue to be used for the solvent of this reaction, favorable results are obtained by adding alcohol solvents such as methanol and ethanol, particularly preferably methanol. The reaction may naturally also be carried out by distilling off the reaction solvent in the first step and using only alcohol solvents such as methanol or ethanol. Metal hydride reducing agents that can be used to carry out the reaction are those which are relatively stable under conditions in which acid is present, examples of which include sodium borohydride, sodium cyanoborohydride, zinc borohydride, sodium triacetoxyborohydride, tetramethylammonium triacetoxyborohydride and borane-pyridine, with sodium cyanoborohydride being used particularly preferably. The reaction temperature is from -20°C to 150°C, and preferably 0°C to 120°C. The 6-N-alkyl-N-benzylamino form obtained here represented with general formula (XI) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{10'}$ and $R^{12'}$ are the same as previously defined) can also be obtained by carrying out the reductive amination process using a metal hydride reducing agent of Chart 2 while using a secondary amine. Moreover, if these processes are carried out using corresponding secondary amines, the compound of general formula (I-B) can also be obtained wherein A is $-NR^{12'}-$.

[0040] In the third step, a benzyl group is removed under hydrogenolytic conditions to form the 6β-amino form (IIaβ2). In this step, good results are obtained by either first convening the substrate to a salt using an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, a sulfonic acid such as methanesulfonic acid, p-toluenesulfonic acid and camphasulfonic acid, or an organic acid such as benzoic acid, acetic acid, oxalic acid and phthalic acid, and preferably hydrochloric acid or phthalic acid, or carrying out the reaction by adding suitable amounts of these acids. Since there are cases in which the resulting secondary amine salt can be purified as a crystal depending on the acid, selection of the acid is important. For example, in the case of a compound wherein R^1 is a cyclopropylmethyl group, $R^{2'}$ and $R^{10'}$ are hydroxy groups, $R^{12'}$ is a methyl group, and $R^{4'}$ is a hydrogen atom, a crystalline salt that can be easily purified is obtained when phthalic acid is used for the acid. Although any solvent can be used for the reaction solvent provided it is inactive under conditions of hydrogenation, examples of which include alcohol solvents such as methanol and ethanol, ether solvents such as THF, ether, DME and dioxane, and aromatic hydrocarbon solvents such as benzene and toluene, alcohol solvents are used preferably and methanol is used particularly preferably. Although all metal catalysts can be used that are normally used in hydrogenation reactions, examples of which include platinum catalysts such as platinum oxide and platinum hydroxide, palladium catalysts such as palladium hydroxide and palladium-carbon, and nickel catalysts such as Raney nickel, a palladium catalyst, and particularly palladium-carbon, is used preferably. Although the reaction can be carried out at a reaction temperature from -30°C to 80°C, and preferably from -10°C to 50°C, and hydrogen pressure from 1 to 100 atmospheres, and preferably from 1 to 30 atmospheres, favorable results are usually obtained at room temperature and normal pressure.

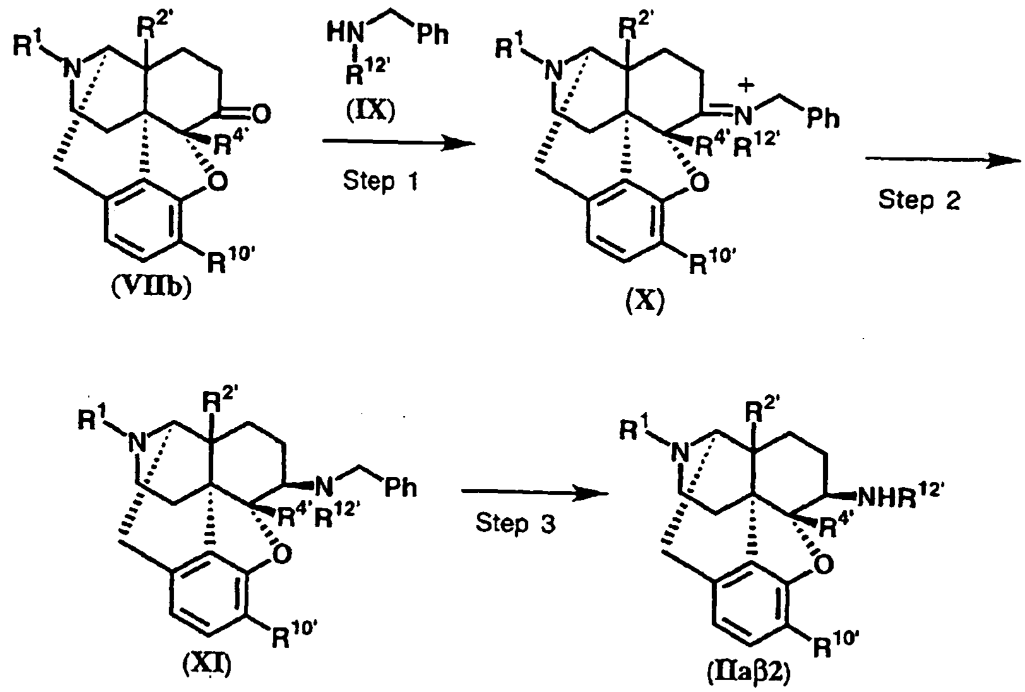


Chart 3

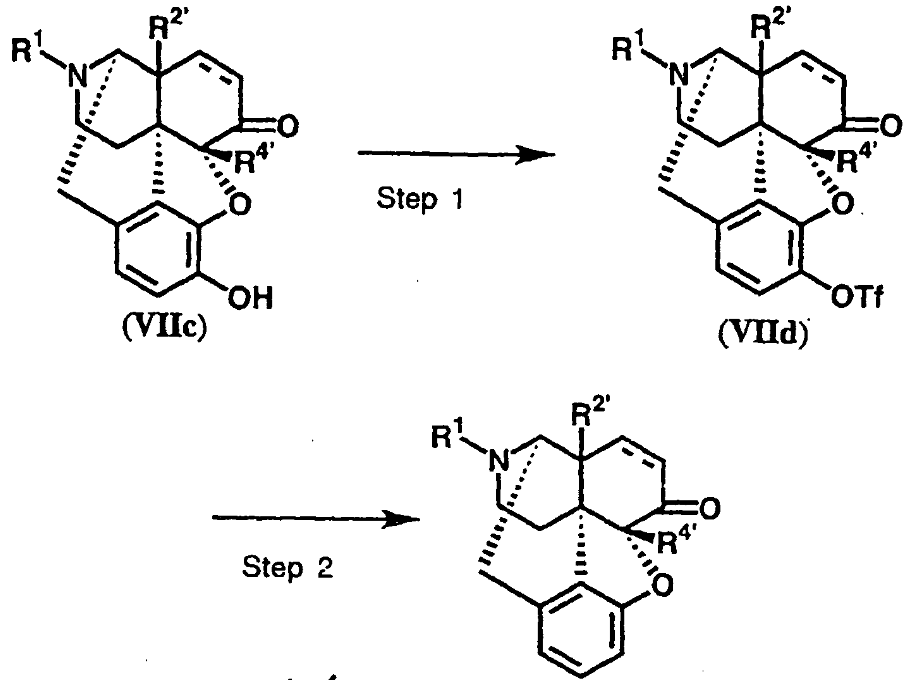
[0041] In addition, in the reductive amination reaction shown in Chart 2, a primary amino form can be obtained by using ammonium acetate instead of primary amine or using dibenzylamine in the process shown in Chart 3, or reducing with borane or under hydrogenation conditions after converting ketone into an oxime using the process described in the literature (J. Med. Chem., 27, 1727 (1984)). This primary amino form can be converted to a secondary amino form by going through two steps consisting of acylation and reduction, and this is useful as a different route for obtaining the secondary amino form.

[0042] Among the 6-amino forms synthesized as shown above, the compound wherein $R^{10'}$ is a hydrogen atom in particular is obtained using a process similar to Charts 2, 3 and 4 and using the 3-dehydroxy-6-keto form represented with general formula (VIIe) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined, for the starting material, which is obtained by using as substrate the 3-hydroxy-6-keto form represented with general formula (VIIc) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined, according to the scheme shown in Chart 6. In addition, the intermediate wherein $R^{10'}$ is a siloxy group is obtained using a process similar to Charts 2, 3 and 4 and using for the starting material the 3-siloxy-6-keto form represented with general formula (VIIf) (wherein R^1, $R^{2'}$ and $R^{4'}$, are the same as previously defined, and G represents an alkylsilyl group) which is obtained from the 3-hydroxy-6-keto form (VIIc) according to the scheme shown in Chart 7.

[0043] Namely, as shown in Chart 6, in the first step for obtaining the 3-dehydroxy-6-keto form represented with general formula (VIIe) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined, trifluoromethanesulfonic anhydride is allowed to act on phenolic hydroxyl groups in the presence of base to obtain the trifrate form represented with general formula (VIId) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined. Although examples of reaction solvents that can be considered include halogen solvents such as dichloromethane and chloroform, ether solvents such as THF, ether, DME and dioxane, and amines having large steric hindrance that can be used as solvents such as 2,6-lutidine and diisopropyl ethyl amine, halogen solvents are used preferably, while dichloromethane is used particularly preferably. Although examples of coexisting bases include tertiary amines such as triethyl amine, diisopropyl ethyl amine and proton sponge®, as well as pyridine, 2,6-lutidine and imidazole, 2,6-lutidine is used preferably. Although the reaction can be carried out at a temperature from -30°C to 50°C, satisfactory results are usually obtained at a temperature from 0°C to room temperature.

[0044] In the second step, the trifrate form is reduced with formic acid in the presence of phosphine ligand and base

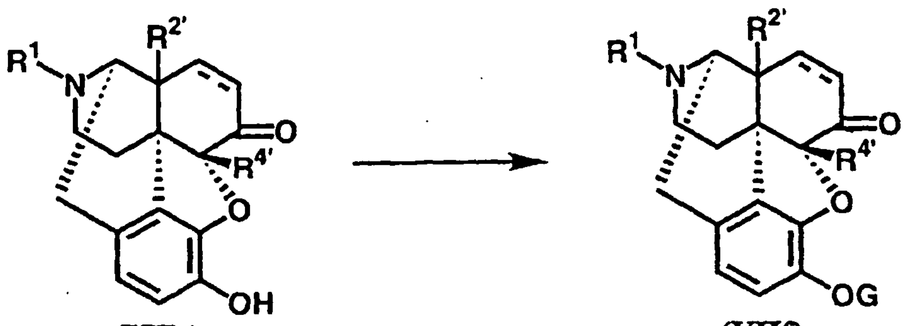
using a palladium catalyst. Although examples of solvents that are used include amines that can be used as solvents such as triethyl amine and diisopropyl ethyl amine, ether solvents such as THF, ether, DME and dioxane, aromatic hydrocarbon solvents such as toluene and benzene, alcohol solvents such as methanol and ethanol, and aprotic dipolar solvents such as DMF and DMSO, DMF is used particularly preferably. Although examples of palladium catalysts that are frequently used include zero-valency complexes such as tetrakis(triphenylphosphine) palladium and bis(benzylidenacetone) palladium, and bivalent complexes such as palladium acetate and palladium chloride, palladium acetate is used normally. Although examples of phosphine ligands used include monodentate phosphines such as trimethylphosphine, triethylphosphine, triphenylphosphine and tris(o-tolu)phosphine, and bidentate phosphines such as bis(diphenylphosphino)methane, 1,2-bis-(diphenylphosphino)ethane, 1,3-bis-(diphenylphosphino)propane and 1,1'-bis-diphenylphosphino ferrocene, 1,1'-bis-diphenylphosphino ferrocene is used particularly preferably. Although examples of coexisting bases include amines such as triethyl amine and diisopropyl ethyl amine, and inorganic salts such as silver carbonate, sodium acetate and potassium acetate, triethyl amine is used preferably. Although the reaction can be carried out at a temperature from 0°C to 150°C, satisfactory results are usually obtained from room temperature to 80°C.



(VIIc) (VIId) (VIIe)

Chart 6

[0045] As shown in Chart 7, in order to obtain the 3-siloxy-6-keto form represented with general formula (VIIf) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined, and G represents an alkylsilyl group), the 3-hydroxy-6-keto form represented with general formula (VIIc) (wherein R^1, $R^{2'}$ and $R^{4'}$ are the same as previously defined) should be reacted with silylchloride in the presence of base. Although examples of silyl chlorides include trimethylsilyl chloride, triphenylsilyl chloride, t-butyldimethylsilyl chloride and diphenylmethylsilyl chloride, t-butyldimethylsilyl chloride is used preferably. Although examples of bases that are used include tertiary amines such as triethyl amine, diisopropylethyl amine and proton sponge®, as well as pyridine, dimethylaminopyridine and imidazole, imidazole is used preferably. Although examples of reaction solvents include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, ether solvents such as ether, THF, DME and dioxane, and pyridine, dichloromethane is used preferably. The reaction can be carried out at a temperature from -80°C to 100°C, and particularly preferably results are obtained in the vicinity of 0°C to room temperature. Although the reaction can be carried out for 5 to 300 minutes, with respect to compounds wherein lines parallel to the solid and broken lines are single bonds and $R^{5'}$ and $R^{6'}$ collectively are -O- in particular, since there are cases in which the 6th position ketone group also ends up being enolsilylated as the reaction time is prolonged, a reaction time of 5 to 60 minutes is preferable.



(VIIc) Chart 7 (VIIf)

[0046] As shown in Chart 8, compounds wherein X is $NR^{12'}$ can be obtained by condensing the 6-amino form obtained in the processes shown in Charts 2 and 3 and represented with general formula (IIa) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{10'}$ and $R^{12'}$ are the same as previously defined) with the carboxylic acid and carboxylic acid derivative represented with general formula (III) (wherein B and $R^{11'}$ are the same as previously defined), the formic acid derivative represented with general formula (IV) (wherein Z, B and $R^{11'}$ are the same as previously defined), the isocyanic acid and isothiocyanic acid derivative represented with general formula (V) (wherein B and $R^{11'}$ are the same as previously defined), or the sulfonic acid derivative represented with general formula (VI) (wherein B and $R^{11'}$ are the same as previously defined). Condensation with carboxylic acid derivative can be performed either by reacting the 6-amino form with acid chloride or acid anhydride that reacts in the presence of base, or by reacting with the carboxylic acid itself using N,N'-dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole or bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). From 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of acid chloride or acid anhydride are used. Although examples of reaction solvents that are used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, ether solvents such as ether, THF, DME and dioxane, pyridine, water or a mixed solvent of the above, chloroform or a mixed solvent of THF and water is used particularly preferably when using acid chloride, while pyridine is used particularly preferably as both base and solvent in the case of using acid anhydride.

[0047] Although examples of bases that are used include tertiary amines such as triethyl amine, diisopropylethyl amine and proton sponge, organic bases such as pyridine, dimethylaminopyridine and imidazole, and inorganic bases such as potassium carbonate, sodium carbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide, satisfactory results are usually obtained using from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of triethyl amine when using chloroform as the solvent, and from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of potassium carbonate, sodium carbonate or sodium bicarbonate in the case of using a mixed solvent of THF and water. The reaction can be carried out over a range of -80°C to 100°C, and particularly preferable results are obtained from 0°C to room temperature. In the case of using DCC for the condensing agent, from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, are used. Although examples of reaction solvents used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, and ether solvents such as ether, THF, DME and dioxane, dichloromethane and chloroform are used particularly preferably. Although examples of bases present in the reaction include tertiary amines such as triethyl amine, diisopropylethyl amine and proton sponge, and organic bases such as pyridine, dimethylaminopyridine and imidazole, from 0.01 to 2 equivalents of dimethylaminopyridine is used particularly preferably. Although the reaction can be carried out over a range of -80°C to 100°C, particularly preferable results are obtained in the vicinity of 0°C to room temperature. In the case of using 1,1'-carbonyldiimidazole for the condensing agent, from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, are used. Although examples of reaction solvents that are used include ether solvents such as ether, THF, DME and dioxane, and halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, THF is used particularly preferably. Although the reaction can be carried out over a range of -20°C to 120°C, a temperature in the vicinity of room temperature to 100°C is particularly preferable. In the case of using BOPCl for the condensing agent, from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, are used. Although examples of reaction solvents that are used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, and ether solvents such as ether, THF, DME and dioxane, dichloromethane and chloroform are used preferably. Although examples of base present in the reaction include tertiary amines such as triethyl amine, diisopropylethyl amine, proton sponge and N-ethylpiperidine, and organic bases such as pyridine, dimethylaminopyridine and imidazole, from 1 to 20 equivalents, and preferably from 1 to 5 equivalents of N-ethylpiperidine is used particularly preferably. Although the reaction can be

carried out over a range of -80°C to 100°C, particularly preferable results are obtained at a temperature from 0°C to 50°C.

[0048] Condensation with formic acid can be performed by reacting the 6-amino form with from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of corresponding acid chloride in the presence of base. Although examples of reaction solvents that are used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, ether solvents such as ether, THF, DME and dioxane, pyridine, water, as well as mixed solvents of these, chloroform or a mixed solvent of THF and water is used particularly preferably. Although examples of bases that are used include tertiary amines such as triethyl amine, diisopropylethyl amine and proton sponge, organic bases such as pyridine, dimethylaminopyridine and imidazole, and inorganic bases such as potassium carbonate, sodium carbonate and sodium bicarbonate, satisfactory results are usually obtained by using from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of triethyl amine when using chloroform for the solvent, and from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, or potassium carbonate, sodium carbonate or sodium bicarbonate in the case of a mixed solvent of THF and water. Although the reaction can be carried out over a range of -80°C to 100°C, particularly preferable results are obtained in the vicinity of 0°C to room temperature.

[0049] Condensation with isocyanic acid or isothiocyanic acid derivative can be performed by allowing from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of the corresponding isocyanate to act on the 6-amino form. Although examples of reaction solvents that are used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, and ether solvents such as ether, THF, DME and dioxane, chloroform is used particularly preferably. Although the reaction can be carried out over a range of -80°C to 100°C, particularly preferable results are obtained in the vicinity of 0°C to room temperature.

[0050] Condensation with sulfonic acid derivative can be performed by allowing from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of the corresponding sulfonyl chloride to act on the 6-amino form. Although examples of bases that are used include tertiary amines such as triethyl amine, diisopropylethyl amine and proton sponge, as well as pyridine, dimethylaminopyridine and imidazole, while examples of reaction solvents that are used include halogen solvents such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane, ether solvents such as ether, THF, DME and dioxane, as well as pyridine, pyridine is used particularly preferably as both base and solvent. Although the reaction can be carried out over a range of -80°C to 100°C, particularly preferable results are obtained in the vicinity of 0°C to room temperature.

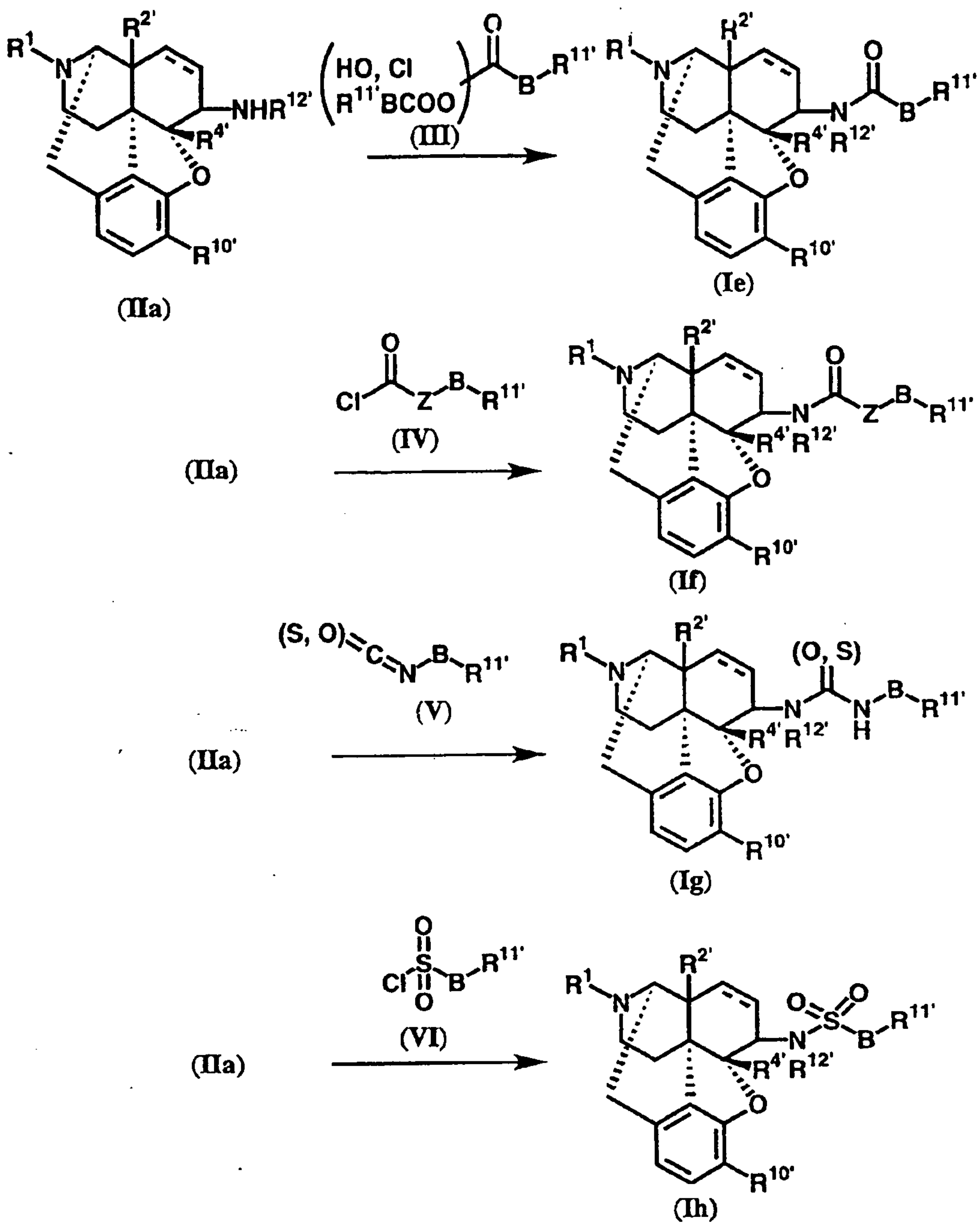


Chart 8

[0051] Since there are cases in which phenolic hydroxyl groups may react at the same time, particularly in the case of compounds wherein $R^{10'}$ is a hydroxy group, in the case of carboxylic acid derivatives, formic acid derivatives, and isocyanic acid or isothiocyanic acid derivatives, after performing the first step in the same manner as Chart 8, the target compound can be obtained by performing alkaline treatment for the second step as shown in Charts 9 through 11.

Although examples of reaction solvents used in the second step include water, alcohol solvents such as methanol and ethanol, ether solvents such as ether, THF, DME and dioxane, or mixed solvents of these, when solubility is insufficient, halogen solvents such as dichloromethane and chloroform can be suitably added. Although examples of bases used include inorganic bases such as potassium carbonate, sodium carbonate, sodium bicarbonate, sodium hydroxide and potassium hydroxide, normally from 1 to 20 equivalents, and preferably from 1 to 10 equivalents, of potassium carbonate or sodium hydroxide are used. Although the reaction can be carried out over a range of -80°C to 100°C, particularly preferably results are obtained at a temperature of from 0°C to 50°C.

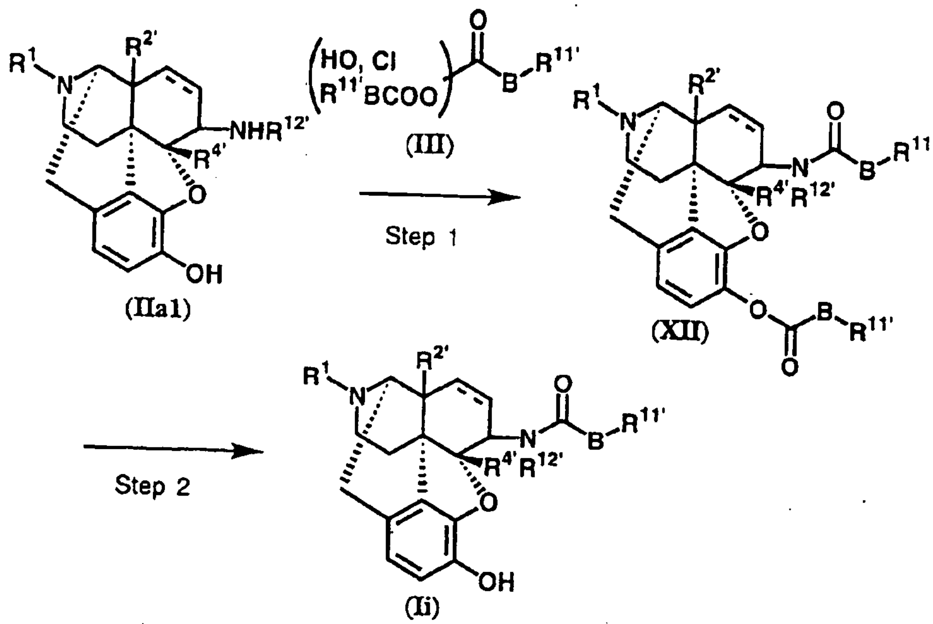


Chart 9

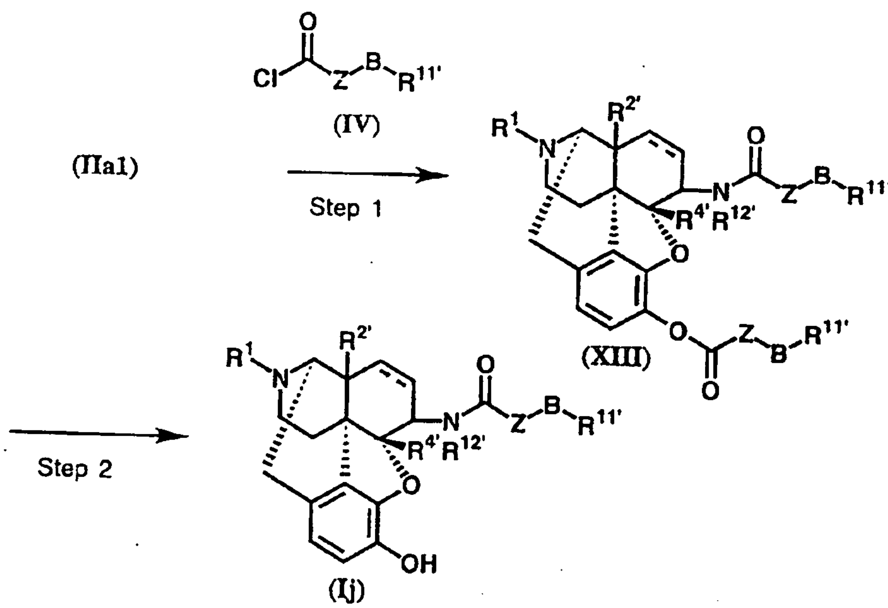


Chart 10

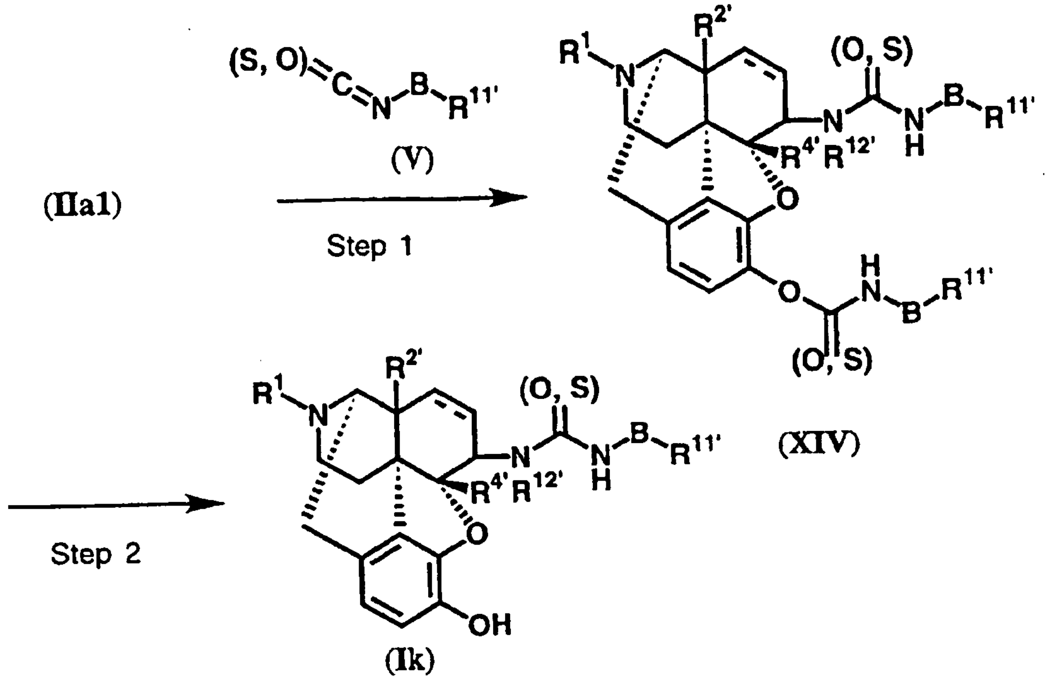
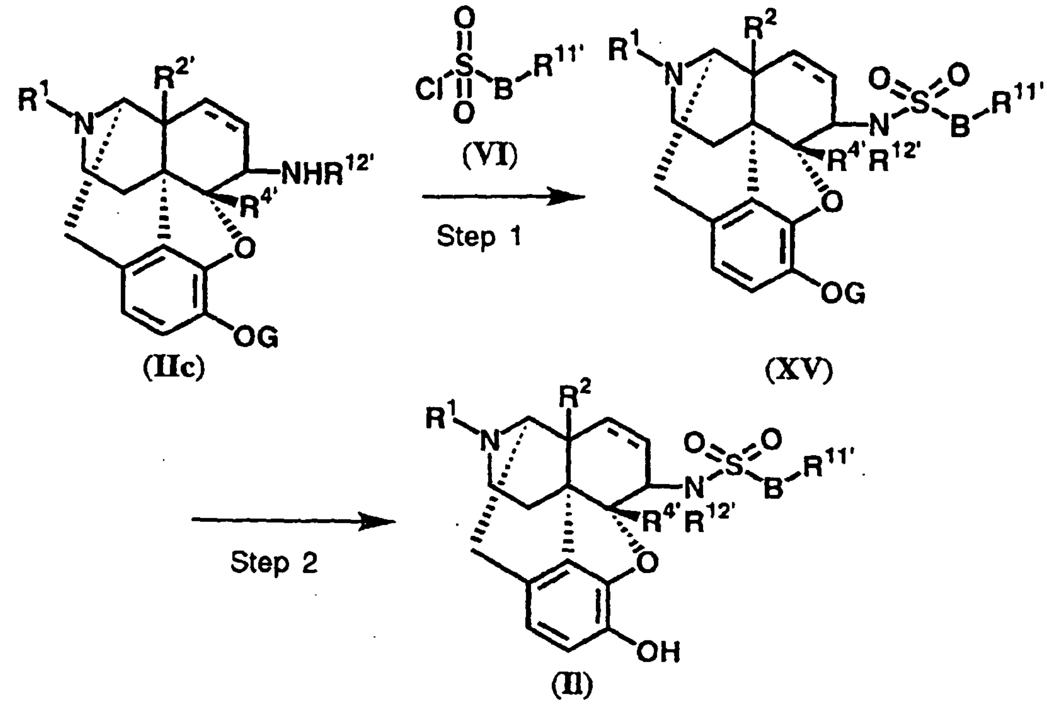


Chart 11

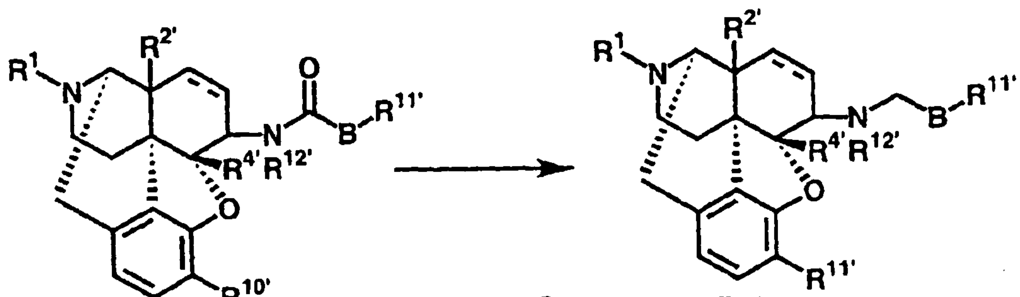
[0052] When condensing a compound wherein $R^{10'}$ is a hydroxy group with a sulfonic acid derivative, preferable results are obtained by using the 3-siloxy-6-amino form represented with general formula (IIc) (wherein R^1, $R^{2'}$, $R^{4'}$, $R^{12'}$ and G are the same as previously defined) in which phenolic hydroxyl groups have been protected in advance with silylether as shown in Chart 12. The following process can naturally also be applied to condensation with carboxylic acid derivatives, formic acid derivatives, and isocyanic acid or isothiocyanic acid derivatives. Namely, after performing the first step in the same manner as Chart 8, the silyl group is removed. Although a quaternary ammonium salt such as tetrabutylammonium fluoride, tetrabutylammonium chloride or pyridinium hydrofluoride, or acid such as acetic acid, hydrochloric acid, sulfuric acid or hydrofluoric acid is used for removal of the silyl group in the second step, normally from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of tetrabutylammonium fluoride are used. Although examples of solvents used include ether solvents such as THF, ether, DME and dioxane, halogen solvents such as dichloromethane and chloroform, and acetonitrile, THF is used particularly preferably. Although the reaction can be performed at a temperature from -20°C to 100°C, satisfactory results are usually obtained at room temperature.



(IIc) (XV) (II)

Chart 12

[0053] In addition, the 6-amino form represented with general formula (Im) in which A' is -NR$^{12'}$- (wherein R^1, R$^{2'}$, R$^{4'}$, B, R$^{10'}$, R$^{11'}$ and R$^{12'}$ are the same as previously defined) is obtained by reducing the amido form represented with general formula (Ie') (wherein R^1, R$^{2'}$, R$^{4'}$, R$^{10'}$, R$^{11'}$, R$^{12'}$ and B are the same as previously defined) using metal hydride catalyst as shown in Chart 13. Examples of reducing agents used include metal hydride compounds having powerful reducing ability such as lithium aluminum hydride, diisobutyl aluminum hydride, aluminum hydride, lithium borohydride and diborane, with from 1 to 20 equivalents, and preferably from 1 to 5 equivalents, of diborane used particularly preferably. Although examples of solvents used preferably when using lithium aluminum hydride, lithium borohydride or diborane include ether solvents such as THF, DME, ether and dioxane, THF is used particularly preferably. When using diisobutyl aluminum hydride or aluminum hydride, aromatic hydrocarbon solvents such as benzene and toluene are used preferably. Although the reaction can be carried out over a range of -40°C to 100°C, a temperature in the vicinity of 0°C to room temperature is particularly preferable.



(Ie') Chart 13 (Im)

[0054] The free base obtained in the above steps can specifically be converted into a salt with a pharmacologically acceptable acid using the process indicated below. Namely, after dissolving or suspending the resulting free base in solvent and adding acid, either the precipitated solid or crystal is obtained by filtration, or in the case of not precipitating, the resulting salt is settled by addition of solvent of lower polarity or substituted with a solvent of lower polarity followed by obtaining by filtration. Alternatively, after forming the salt as described above, the salt can be obtained by concentration. However, in the case organic solvent remains in these processes, the residual solvent can also be removed under reduced pressure after freeze-drying as an aqueous solution. Although examples of solvents used for dissolution or suspension include water, alcohol solvents such as methanol, ethanol and isopropyl alcohol, halogen solvents such as dichloromethane and chloroform, ether solvents such as ether, THF, DME and dioxane, ester solvents such as ethyl acetate and methyl acetate, or mixed solvents of these, methanol, ethanol, isopropyl alcohol, ethyl acetate, chloroform, chloroform-methanol, water-methanol and water-ethanol are used preferably. Preferable examples of solvents used for precipitating the solid include ether and ethyl acetate. Although it is desirable to add acid to match the equivalent as much as possible, in cases in which the resulting salt is washed and the excess acid can be removed, from 1 to 10 equivalents may be used. In addition, the acid may be added directly or added after suitably dissolving in the above-mentioned solvents. For example, hydrochloric acid can be added in the form of concentrated hydrochloric acid, a 1 N aqueous solution, a saturated methanol solution or a saturated ethyl acetate solution, while tartaric acid can be added in the form of a solid, aqueous solution or methanol solution. During salt formation, since the temperature of the system may rise due to the heat of neutralization, there are cases in which preferable results are obtained by cooling with a water bath or ice bath.

[0055] As a result of both in vitro and in vivo pharmacological studies, the compounds of the present invention represented with general formula (I) were found to possess strong analgesic activity, diuretic activity, antitussive activity as an opioid κ-agonist. It thus became clear that said compounds can be expected to be useful analgesics, diuretics and antitussives. In addition, based on their properties of being κ-agonists, they can also be used as hypotensives and sedatives. Moreover, it was also found that selective agonists for δ receptors are also included in the compounds of the present invention, thus suggesting their possible use as immunostimulator and anti-HIV drugs. On the other hand, since these compounds also demonstrate excellent defensive effects against cerebral nerve cell necrosis, they can also be used as cerebro-neuroprotective agents for prevention and treatment of ischemic brain damage and dementia based on damage to cerebral nerve cells.

[0056] More specifically, the compounds of the present invention are useful in pharmaceutical fields as preventive and therapeutic agents for post-operative pain, carcinomatous pain and other broad-ranging, general pain, hypertension, edema and promotion of urination during gestosis, various types of respiratory diseases such as colds, acute bronchitis, chronic bronchitis, bronchiectasis, pneumonia, pulmonary tuberculosis, silicosis and silicotic tuberculosis, lung cancer, upper respiratory tract diseases (pharyngitis, laryngitis, nasal catarrh), asthmatic bronchitis, bronchial asthma, infantile asthma, (chronic) pulmonary emphysema, pneumoconiosis, fibroid lung, silicosis, pulmonary suppuration, pleurisy, tonsillitis, tussive urticaria and pertussis, suppression of coughing during bronchography and accompanying bronchoscopic examinations, and as preventive and therapeutic agent for cerebrovascular diseases such as cerebral hemorrhage, stroke, cerebral infarction and subarachnoid hemorrhage; as preventive and therapeutic agents for sequela based on these cerebral nerve cell disorders (consciousness disorders, motor paralysis, language disorders, sensory disorders, mental disorders and memory disorders); as preventive and therapeutic agents for neural diseases such as hypoxia, hypoglycemia, cerebral palsy, cerebral ischemic stroke and Huntington's chorea; as preventive and therapeutic agents for cerebroneural function diseases such as senile dementia, Alzheimer's dementia, amnesia and cerebroneural disorders; suppression of activated oxygen disorders; and as preventive and therapeutic agents for degenerative nerve diseases such as epilepsy, depression and Parkinson's disease.

[0057] When the analgesic diuretic, antitussive or cerebro-neuroprotective agents of the present invention is used clinically, it may be in the form of a free base or its salt. In addition, it may also be suitably mixed with stabilizers, buffers, diluents, isotonics, antiseptics and other vehicles. Examples of administrative forms include injection preparations; oral preparations such as tablets, capsules, granules, powders and syrups; transrectal administration by suppositories; or local administration by ointments, creams and compresses. It is desirable that the analgesic, diuretic, antitussive and cerebro-neuroprotective agents of the present invention contain from 1% to 90% by weight, and preferably from 30% to 70% by weight, of the above-mentioned active ingredients. Although the dose should be suitably selected according to symptoms, age, body weight and administration method, the normal adult dose is from 0.0001 mg to 1 g per day as the amount of active ingredient in the case of injection preparations, and from 0.005 mg to 10 g in the case of oral preparations, each administered in a single dosing or divided among several dosings.

EXAMPLES

[0058] Although the following provides an explanation of the present invention in the form of the specific examples described below, the present invention is not limited to these examples.

[Reference Example 1]

N-Acetylbenzylamine

[0059] 10 g of benzylamine was dissolved in 200 ml of methylene chloride followed by the addition of 26 ml of triethylamine and dropwise addition of 7.3 ml of acetyl chloride at 0°C. After stirring for 1 hour at room temperature, 2 ml of methanol was added to the reaction system at 0°C followed by 120 ml of water and separation of the phases. The aqueous layer was extracted with 100 ml of chloroform, and the resulting organic layer was concentrated after drying with anhydrous sodium sulfate to obtain 8.55 g of the target compound (yield: 61%).
NMR (90 MHz, $CDCl_3$)

δ 1.9 (3H, s), 4.3 (2H, d, J=4.8 Hz), 6.8 (1H, br s), 7.3 (5H, s).

IR (liquid film method)

ν 3296, 1649, 1543, 1499, 1377, 1359, 1284, 1077, 1033 cm^{-1}

[Reference Example 2]

N-Benzylethylamine

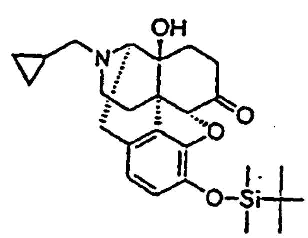
[0060] 2.96 g of the N-acetylbenzylamine obtained in reference example 1 was dissolved in 45 ml of anhydrous tetrahydrofuran followed by the addition of 1.73 g of lithium aluminum hydride at 0°C. After stirring for 2 hours at room temperature, the reaction mixture was refluxed while heating for 2 hours. After cooling the reaction mixture to 0°C, 22.8 g of sodium fluoride was added followed by dropwise addition of 91 ml of 10% aqueous tetrahydrofuran and stirred for 1 hour at room temperature. The precipitate was removed using Celite and the filtrate was concentrated to obtain 2.5 g of the target compound in liquid form (yield: 93%).

δ 1.10 (3H, t, J=7.3 Hz), 1.4 (1H, brs), 2.65 (2H, q, J=7.3 Hz), 3.75 (2H, s), 7.15-7.4 (5H, m).

[Reference Example 3]

3-tert-butyldimethylsilyloxy-17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-6-oxomorphinan 2

[0061]



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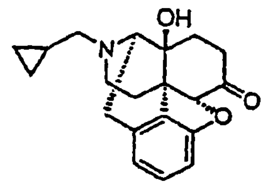
[0062] 3.49 g of naltrexone hydrochloride was suspended in 10.5 ml of N,N-dimethylformamide. After adding 3.46 g of imidazole, 3.48 g of tert-butyldimethylchlorosilane was added followed by stirring for 35 minutes at room temperature. 30 ml of water and 50 ml of diethyl ether were added to the reaction system followed by separation. The aqueous layer was extracted twice with 30 ml of diethyl ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated. The resulting residue was recrystallized from ethanol to obtain 3.2 g of the target compound (yield: 76%).
NMR (90 MHz, $CDCl_3$)

δ 0.0-1.2 (5H, m), 0.2 (3H, s), 0.3 (3H, s), 1.0 (9H, s), 1.3-2.0 (3H, m), 2.0-3.2 (8H, m), 2.4 (2H, d, J=4.4 Hz), 4.60 (1H, s), 6.5 (1H, d, J=6.4 Hz), 6.6 (1H, d, J=6.4 Hz).

[Reference Example 4]

3-Dehydroxynaltrexone 3

[0063]



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[0064] Naltrexone (5 g) was dissolved in dichloromethane (50 ml) followed by the addition of 2,6-lutidine (2.56 ml) and anhydrous trifluoromethanesulfonic acid (2.96 ml) at 0°C. After reacting for 15 minutes at the same temperature, distilled water (40 ml) and saturated aqueous sodium bicarbonate (20 ml) were added followed by extraction with chloroform (20 + 30 ml). After washing with saturated brine, the extracts was dried with anhydrous sodium sulfate and the solvent was distilled off. Ether (20 ml) was added and the precipitating solid was filtered out using Celite followed by initial purification with silica gel column chromatography (Merk 7734, 300 g; chloroform → 1% methanol/chloroform).

[0065] The initially purified product was dissolved in anhydrous DMF (25 ml) and reacted with triethylamine (5.9 ml), palladium acetate (0.06 g), DPPF (0.16 g) and formic acid (1.1 ml) for 15 minutes at 60°C. After distilling off the solvent, saturated aqueous sodium bicarbonate (20 ml) and distilled water (10 ml) were added followed by extraction with chloroform (30 ml x 2). After washing with saturated brine and drying with anhydrous sodium sulfate, the solvent was distilled off and the resulting black oily substance was purified with silica gel column chromatography (Merk 7734, 300 g; chloroform) to obtain the target compound (3.32 g, yield: 62%).

NMR (400 MHz, $CDCl_3$)

δ 0.26 (2H, m), 0.57 (2H, m), 0.88 (1H, m), 1.54 (1H, dd, J=12.7, 2.0 Hz), 1.63 (1H, dt, J=14.7, 3.9 Hz), 1.89 (1H, m), 2.13 (1H, dt, J=12.7, 3.9 Hz), 2.31 (1H, dt, J=14.7, 2.9 Hz), 2.42 (3H, m), 2.63 (1H, dd, J=18.6, 5.7 Hz), 2.70 (1H, dd, J=12.7, 4.9 Hz), 3.04 (1H, dt, J=14.7, 4.9 Hz), 3.11 (1H, d, J=19.5 Hz), 3.21 (1H, d, J=5.9 Hz), 4.65 (1H, s), 5.0-5.5 (1H, br), 6.69 (1H, d, J=6.8 Hz), 6.75 (1H, d, J=6.8 Hz), 7.07 (1H, t, J=6.8 Hz)

IR (neat)

ν 3406, 1729, 1630, 1607, 1458, 1052, 938, 781 cm^1

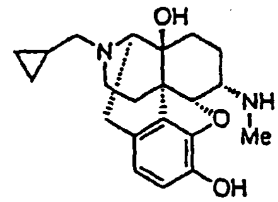
Mass (EI)

m/z 325 (M+)

[Reference Example 20]

17-Cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4

[0066]



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[0067] Naltrexone (1.0 g) and methylamine hydrochloride (0.99 g, 5 equivalents) were dissolved in methanol (15 ml) followed by stirring for 20 minutes at room temperature. This reaction solution was added to platinum oxide (0.05 g, 5 w%) in methanol (10 ml) activated in advance in a hydrogen atmosphere followed by hydrogenation for 4 hours at room temperature and atmospheric pressure. The catalyst was removed by Celite filtration and the solvent was distilled off. After adding saturated aqueous sodium bicarbonate (20 ml) and extracting with chloroform (20 ml x 2), the extract was washed with saturated brine and dried with anhydrous sodium sulfate, and the solvent was distilled off. The resulting dark reddish-violet oily substance was dissolved in chloroform (2 ml) followed by addition of ethyl acetate (4 ml) to obtain the target compound (0.83 g, yield: 79%) by crystallization. A portion of this compound was removed and various spectra were measured in the form of a hydrochloride.
mp 270°C (decomposition)
NMR (500 MHz, DMSO-d_6)

δ 0.40 (1H, m), 0.48 (1H, m), 0.61 (1H, m), 0.69 (1H, m), 0.95 (1H, m), 1.08 (1H, m), 1.47 (1H, m), 1.70 (1H, d, J=13.2 Hz), 1.81 (1H, m), 1.92 (1H, m), 2.49 (1H, m), 2.68 (3H, s), 2.72 (1H, m), 3.00 (1H, m), 3.08 (2H, m), 3.26 (2H, m), 3.57 (1H, m), 4.01 (3H, m), 4.97 (1H, brs), 6.50 (1H, s), 6.65 (1H, d, J=8.3 Hz), 6.78 (1H, d, J=8.3 Hz), 9.20 (2H, m)

1R (KBr)

ν 3200, 1510, 1464, 1238, 1116, 982, 859 cm^{-1}.

Mass (EI)

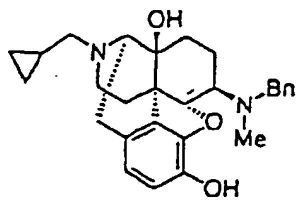
m/z 356 (M+) (measured in the free form)

Elementary Analysis: As $C_{21}H_{28}N_2O_3 \cdot 2HCl \cdot 0.2H_2O$				
Calculated values:	C 58.25;	H 7.08;	N 6.47;	Cl 16.38
Measured values:	C 58.35;	H 7.20;	N 6.44;	Cl 16.14

[Reference Example 21]

6β-(N-Benzyl)methylamino-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydxoxymorphinan 8

[0068]



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[0069] 10.1 g of Naltrexone hydrochloride was separated with 150 ml of a 4:1 solution of chloroform and methanol and 150 ml of saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with 100 ml of a 4:1 solution of chloroform and methanol. The resulting organic layer was dried with anhydrous sodium sulfate followed by the addition of 3.26 g of benzoic acid and concentration after completely dissolving. After adequately drying the residue with a vacuum pump, the residue was suspended in 400 ml of benzene. After adding 5.2 ml of benzylmethylamine, 4.9 g of benzoic acid and 0.23 g of p-toluenesulfonic acid, the resulting mixture was stirred for 18 hours in a 110°C oil bath while boiling off the water. After distilling off 330 ml of benzene at atmospheric pressure, 330 ml of ethanol and 4 g of molecular sieves 4A were added to the reaction mixture followed by cooling to 0°C. Next, 2.52 g of sodium cyanoborohydride was added followed by stirring for 2 hours at room temperature. After adding 200 ml of methanol to the reaction system, the molecular sieves was filtered out and the filtrate was concentrated. 200 ml of chloroform and 150 ml of saturated aqueous sodium bicarbonate were added to the resulting residue and the resulting precipitate was filtered followed by separation. The aqueous layer was extracted twice with 100 ml of chloroform, and the organic layer was concentrated after drying with anhydrous sodium sulfate. The resulting crude product was purified with silica gel column chromatography (480 g ammonia saturated ammonium chloroform/chloroform = 2/1) to obtain 10.87 g of the oily target compound (yield: 91%). This was then recrystallized from methanol.

mp 71-80°C (decomposition)
NMR (400 MHz, $CDCl_3$)

δ 0.09-0.13 (2H, m), 0.49-0.55 (2H, m), 0.79-0.88 1.59-1.66 (2H, m), 1.87-2.00 (1H, m), 2.11 (1H, dt, J=3.4, 11.7 Hz), 2.19-2.27 (1H, m), 2.34 (3H, s), 2.35 (2H, d, J=6.8 Hz), 2.50-2.59 (1H, m), 2.56 (1H, dd, J=5.4, 18.1 Hz), 2.62 (1H, dd, J=4.4, 11.7 Hz), 2.99 (1H, d, J=18.1 Hz), 3.04 (1H, d, J=5.4 Hz), 3.53 (1H, d, J=13.2 Hz), 3.82 (1H, d, J=13.7 Hz), 4.68 (1H, d, J=8.3 Hz), 6.51 (1H, d, J=8.3 Hz), 6.65 (1H, d, J=8.3 Hz), 7.20-7.35 (5H, m).

IR (KBr)

ν 3428, 3220, 1638, 1615,1502, 1458, 1375, 1330, 1238, 1147, 1116, 1033, 990, 917, 857, 735 cm^{-1}

Mass (EI)

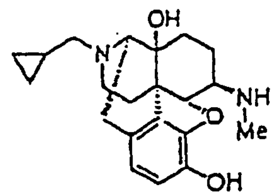
m/z 446 (M+), 355, 286, 160.

Elementary Analysis: AS $C_{28}H_{34}N_2O_3 \cdot 0.5H_2O$			
Calculated values:	C, 73.82;	H, 7.74;	N, 6.15.
Measured values:	C, 73.94;	H, 7.79;	N, 6.08.

[Reference Example 22]

17-Cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10

[0070]



10

[0071] 12.65 g of 6β-(N-benzyl)methylamino-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxymorphinan 8 • 2 hydrochloride (converted to a hydrochloride by established methods) was dissolved in 250 ml of methanol followed by the addition of 2.53 g of 5% palladium-carbon and stirring for 4 hours in a hydrogen atmosphere. After removing the catalyst using Celite, the filtrate was concentrated. 100 ml of a 4:1 solution of chloroform and ethanol and 100 ml of saturated aqueous sodium bicarbonate were added to the resulting residue to separate, and the aqueous layer was then extracted twice with 100 ml of a 4:1 solution of chloroform and ethanol. After drying the organic layer with anhydrous sodium sulfate, the dried organic layer was concentrated to obtain 8.00 g of crude product. This was then recrystallized from methanol to obtain 5.84 g of the target compound (yield: 67%).
NMR (400 MHz, $CDCl_3$)

δ 0.10-0.14 (2H, m), 0.50-0.55 (2H, m), 0.79-0.86 (1H, m), 1.38 (1H, dt, J=2.9 Hz, 12.8 Hz), 1.41-1.48 (1H, m), 1.58-1.72 (2H, m), 1.78-1.91 (1H, m), 2.08-2.25 (2H, m), 2.36 (1H, d, J=6.6 Hz), 2.45 (3H, s), 2.49-2.65 (3H, m), 3.00 (1H, d, J=18.3 Hz), 3.05 (1H, d, J=5.9 Hz), 4.48 (1H, d, J=7.7 Hz), 6.54 (1H, d, J=8.1 Hz), 6.66 (1H, d, J=8.1 Hz).

IR (KBr)

ν 3380, 2926, 1638, 1607, 1462, 1255, 1180, 795 cm^{-1}.

Mass (EI)

m/e 356 M+

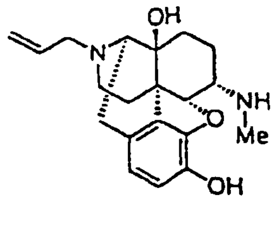
Elementary Analysis: $C_{21}H_{28}O_3N_2$			
Calculated values:	C, 70.76;	H, 7.92;	N, 7.86.
Measured values:	C, 70.51;	H, 7.94;	N, 7.84.

[Reference Example 6]

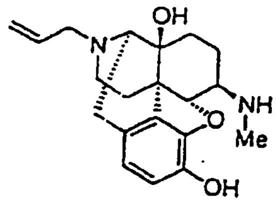
17-Allyl-3,14β-dihydroxy-4,5α-epoxy-6α-methylaminomorphinan 12

17-Allyl-3,14β-dihydroxy-4,5α-epoxy-6β-methylaminomorphinan 13

[0072]



12



13

[0073] Naloxone hydrochloride (3.0 g), methylamine hydrochloride (5.57 g) and sodium cyanoborohydride (0.33 g) were suspended in anhydrous methanol (40 ml) and stirred for 17 hours at room temperature. After addition of concentrated hydrochloric acid (1.0 ml) and removal of solvent by distillation, distilled water (50 ml) was added followed by washing with chloroform (20 ml). Saturated aqueous sodium bicarbonate (10 ml) was added to make the solution basic followed by extraction with chloroform (30 ml x 3). After drying with anhydrous magnesium sulfate, the solvent was distilled off. The resulting crude product was purified with silica gel column chromatography (Merk 7734 100 g; ethyl acetate/methanol/aqueous ammonia = 90/10/1->80/20/2) to obtain the target compound in the form of a pure fraction (12 0.4 g, 12%; 13 0.8 g, 24%).

Compound 12

[0074] NMR (400 MHz, $CDCl_3$)

δ 0.87 (1H, m), 1.39 (1H, m), 1.66 (3H, m), 2,19 (1H, dt, J=12.2, 4.9 hz), 2.29(1H, dt, J=12.7, 3.4 Hz), 2.55 (3H, m), 2.59 (3H, s), 2.90 (1H, d, J=6.4 Hz), 3.09 (2H, m), 3.18 (1H, m), 4.76 (1H, d, J=3.4 Hz), 4.7-4.9 (1H, br), 5.17 (2H, m), 5.80 (1H, m), 6.50 (1H, d, J=7.8 Hz), 6.69 (1H, d, J=7.8 Hz)

IR (neat)

ν 3400, 1618, 1450, 1386, 1160, 1067, 750 cm^{-1}.

Mass (EI)

m/z 342 (M+)

Compound 13

[0075] NMR (500 MHz, $CDCl_3$)

δ 1.42 (2H, m), 1.61 (2H, m), 1.91 (1H, dq, J=12.8, 3.1 Hz), 2.16 (2H, m), 2.47 (3H, s), 2.56 (3H, m), 2.87 (1H, d, J=5.5 Hz), 3.03 (1H, d, J=18.3 Hz), 3.11 (2H, d, J=6.7 Hz), 4.51 (1H, d, J=7.9 Hz), 4.7-5.2 (3H, br), 5.18 (2H, m), 5.79 (1H, m), 6.55 (1H, d, J=7.9 Hz), 6.64 (1H, d, J=7.9 Hz)

IR (neat)

ν 3400, 1560, 1543, 1458, 1255, 1036, 731 cm^{-1}.

Mass (EI)

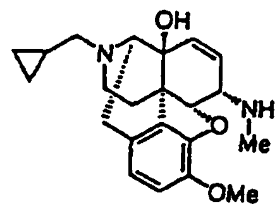
m/z 342 (M+)

[Reference Example 7]

[0076] 17-Cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-14β-hydroxy-3-methoxy-6α-(N-methylamino)morphinan (yield: 40%) 14, and 17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-3-methoxy-6β-(N-methylamino)morphinan (yield: 23%) 15 were obtained by following the procedure of reference example 6 but using 17-cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-14β-hydroxy-3-methoxymorphinan-6-one instead of naloxone hydrochloride.

Compound 14

[0077]



14

NMR (500 MHz, $CDCl_3$)

δ 0.13-0.18 (2H, m), 0.53-0.59 (2H, m), 0.88 (1H, m), 1.78 (1H, d, J=7.8 Hz), 2.38 (2H, d, J=7.8 Hz), 2.40 (1H, d, J=6.3 Hz), 2.44 (1H, dd, J=12.7, 6.3 Hz), 2.50 (1H, dd, J=18.6, 6.8 Hz), 2.58 (3H, s), 2.72 (1H, d, J=7.8 Hz), 3.08 (1H, d, J=18.6 Hz), 3.35 (1H, d, J=6.8 Hz), 3.65 (1H, m), 3.84 (3H, s), 4.97 (1H, br), 4.99 (1H, dd, J=5.9, 1.5 Hz), 5.54 (1H, dd, J=9.8, 2.9 Hz), 5.88 (1H, dt, J=9.8, 1.5 Hz), 6.51 (1H, d, J=7.8 Hz), 6.63 (1H, d, J=7.8 Hz).

IR (neat)

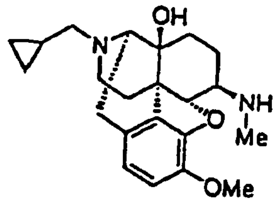
ν 3342, 2938, 1508, 1456, 1284, 1205, 1123, 1054, 1017, 748 cm^{-1}

Mass (EI)

m/z 368 (M+)

Compound 15

[0078]



15

mp 121.5-123.5°C (ethylacetate-ether)
NMR (400 MHz, $CDCl_3$)

δ 0.09-0.16 (2H, m), 0.50-0.56 (2H, m), 0.84 (1H, m), 1.36 (1H, td, J=12.7, 3.9 Hz), 1.44 (1H, dd, J=12.7, 2.4 Hz), 1.61 (1H, dt, J=13.2, 3.4 Hz), 1.66-1.83 (2H, m), 2.10 (1H, td, J=12.2, 3.9 Hz), 2.23 (1H, td, J=12.2, 4.9 Hz), 2.36 (2H, dd, J=6.4, 1.5 Hz), 2.43 (1H, m), 2.48 (3H, s), 2.57-2.66 (2H, m), 3.03 (1H, d, J=18.6 Hz), 3.08 (1H, d, J=5.9 Hz), 3.87 (3H, s), 4.45 (1H, d, J=6.8 Hz), 6.61 (1H, d, J=8.3 Hz), 6.72 (1H, d, J=8.3 Hz).

IR (KBr)

ν 3390, 3344, 2944, 2802, 1632, 1611, 1504, 1446, 1282, 1263, 1044, 980, 901 cm^{-1}

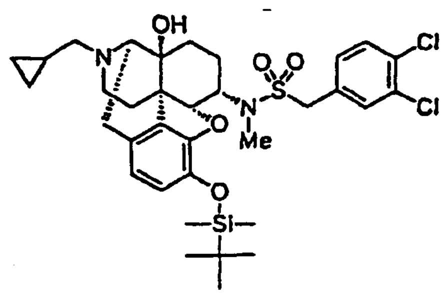
Mass (EI)

m/z 370 (M+).

[Reference Example 8]

3-tert-butyldimethylsilyloxy-17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-6α-(N-methyl-3,4-dichlorophenylmethanesulfonamido)morphinan 16

[0079]



16

[0080] 203.9 mg of 3-tert-butyldimethylsilyloxy-17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-6α-methylaminomorphinan 7 obtained in reference example 5 was dissolved in 3 ml of pyridine followed by the addition of 124 mg of 3,4-dichorophenylmethanesufonylchloride and stirring for 30 minutes at room temperature. After concentrating the reaction system, 3 ml of saturated aqueous sodium bicarbonate and 3 ml of chloroform were added to separate layers, after which the aqueous layer was extracted twice with 3 ml of chloroform. After drying with anhydrous sodium sulfate,

the organic layer was concentrated to obtain the oily crude product. This was then purified with silica gel column chromatography (30 g benzene/ethyl acetate = 5/1) to obtain 235.4 mg of the target compound (yield: 78%).
NMR (500 MHz, $CDCl_3$)

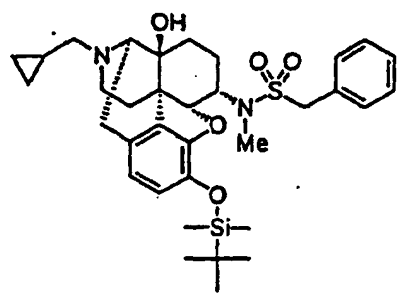
δ 0.09-0.16 (2H, m), 0.15 (3H, s), 0.21 (3H, s), 0.51-0.57 (2H, m), 0.80-0.89 (1H, m), 0.97 (9H, s), 1.21-1.30 (2H, m), 1.42-1.49 (2H, m), 1.71 (1H, dt, J=14.7, 9.5 Hz), 2.15 (1H, dt, J=12.5, 5.1 Hz), 2.22 (1H, dt, J=12.5, 3.7 Hz), 2.30 (1H, dd, J=12.8, 6.6 Hz), 2.35 (1H, dd, J=12.8, 6.6 Hz), 2.56 (1H, dd, J=18.7, 7.0 Hz), 2.60-2.65 (1H, m), 2.89 (3H, s), 3.01 (1H, d, J=18.7 Hz), 3.05 (1H, d, J=7.0 Hz), 4.16 (1H, d, J=13.9 Hz), 4.19 (1H, d, J=13.9 Hz), 4.22-4.28 (1Hm), 4.41 (1H, d, J=3.3 Hz), 4.90 (1H, brs), 6.48 (1H, d, J=8.1 Hz), 6.62 (1H, d, J=8.1 Hz), 7.31 (1H, dd, J=8.1, 2.2 Hz), 7.46 (1H, d, J=8.1 Hz), 7.53 (1H, d, J=2.2 Hz).

Mass (EI)

m/z 692 M+

[Reference Example 9]

[0081] 3-tert-butyldimethylsilyloxy-17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-6α-(N-methylphenylmethanesulfonamido)morphinan 17 (yield: 50%) was obtained by following the procedure of reference example 8 but using phenylmethanesulfonylchloride instead of 3,4-dichlorophenylmethanesulfonylchloride.



17

NMR (500 MHz, $CDCl_3$)

δ 0.08-0.13 (2H, m), 0.14 (3H, s), 0.20 (3H, s), 0.50-0.55 (2H, m), 0.79-0.87 (1H, m), 0.97 (9H, s), 1.10-1.22 (2H, m), 1.37-1.43 (2H, m), 1.64 (1H, dt, J=15.0, 9.5 Hz), 2.12 (1H, dt, J=12.5, 5.1 Hz), 2.20 (1H, dt, J=12.5, 3.3 Hz),2.29 (1H, dd, J=12.5, 6.6 Hz), 2.33 (1H, dd, J=12.5, 6.6 Hz), 2.54 (1H, dd, J=18.7, 7.0 Hz), 2.59-2.63 (1H, m), 2.83 (3H, s), 2.99 (1H, d, J=18.7 Hz), 3.02 (1H, d, J=7.0 Hz), 4.19-4.24 (1H, m), 4.24 (1H, d, J=13.9 Hz), 4.28 (1H, d, J=13.9 Hz), 4.34 (1H, 6., J=2.9 Hz), 4.88 (1H, brs), 6.46 (1H, d, J=8.1 Hz), 6.61 (1H, d, J=8.1 Hz), 7.32-7.40 (3H, m), 7.42-7.47 (2H, m).

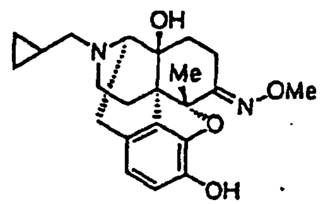
Mass (EI)

m/z 624 M+

[Reference Example 10]

5β-Methylnaltrexone-O-methyloxime(17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-5β-methyl-6-methoxyiminomorphinan) 18

[0082]



18

[0083] 109.3 mg of 5β-methylnaltrexone (0.326 mmol) and 37.2 mg of methoxyamine hydrochloride (0.445 mmol) were dissolved in 1.6 ml of methanol followed by the addition of 0.17 ml of 10% aqueous sodium hydroxide to this solution and refluxing while heating. After 8.5 hours part way through the refluxing period, a solution of 36.1 mg (0.432 mmol) of methoxyamine hydrochloride in 0.5 ml of methanol was added and refluxing was continued until a total of 23 hours had elapsed. After allowing the reaction solution to cool to room temperature by standing, 5 ml of water and 1 ml of saturated aqueous sodium bicarbonate were added followed by extraction with 2 x 5 ml of chloroform. The organic layers were combined and dried with anhydrous sodium sulfate followed by concentration to obtain 107.4 mg of the unpurified target compound. This unpurified compound was used in the following reaction without being purified.
NMR (400 MHz, $CDCl_3$)

δ 0.13 (2H, m), 0.53 (2H, m), 0.84 (1H, m), 1.37 (1H, m), 1.43 (1H, dd, J=14.1, 3.4 Hz), 1.62 (1H, m), 1.71 (3H, s), 2.23-2.30 (3H, m), 2.30 (1H, br s, OH), 2.37 (2H, d, J=6.5 Hz), 2.55 (1H, dd, J=18.3, 6.1 Hz), 2.71 (1H, m), 3.00 (1H, d, J=18.3 Hz), 3.04 (1H, d, J=6.1 Hz), 3.14 (1H, ddd, J=14.7, 3.2, 3.2 Hz), 3.80 (3H, s), 4.95 (1H, br s, OH), 6.55 (1H, d, J=8.0 Hz), 6.70 (1H, d, J=8.0 Hz).

IR (KBr)

ν 3380, 1638, 1620, 1510, 1460, 1377, 1336, 1241, 1118, 1038, 953, 866, 752 cm^{-1}.

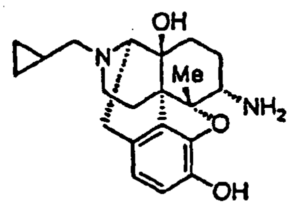
Mass (EI)

m/z 384 (M+).

[Reference Example 11]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-5β-methyl-6α-aminomorphinan 19.

[0084]



19

[0085] 101.0 mg (approximately 0.26 mmol) of the unpurified 5β-methylnaltrencone-O-inethyloxiine 18 obtained in reference example 10 was dissolved in 2.5 ml of anhydrous THF in the presence of argon gas followed by cooling to 0°C. After adding 1.31 ml of an anhydrous THF solution of 1.0 M borane • THF complex to this solution, the solution was refluxed for 18.5 hours while heating. After cooling the reaction solution to 0°C and slowly adding 10 ml of 2 N hydrochloric acid, the solution was again refluxed for 40 minutes while heating. The reaction solution was cooled to 0°C followed by the addition of 4 ml of 5 N aqueous ammonia and 2 ml of saturated aqueous sodium bicarbonate, and extraction with 3 x 5 ml of chloroform-methanol (4:1). The organic layers were combined and dried with anhydrous sodium sulfate followed by concentration to obtain 89.6 mg of the unpurified target compound. This unpurified compound was then used in the following reaction without being purified.
NMR (400 MHz, $CDCl_3$)

δ 0.12 (2H, m), 0.53 (2H, m), 0.83 (1H, m), 1.37-1.84 (5H, m), 1.63 (3H, s), 2.15-2.28 (2H, m), 2.33 (2H, d, J=5.7 Hz), 2.60 (1H, dd, J=18.5, 6.3 Hz), 2.67 (1H, m), 2.99 (1H, d, J=18.5 Hz), 3.00 (3H, br s, OH, NH2), 3.02 (1H, d, J=6.3 Hz), 3.14 (1H, dd, J=8.8, 3.8 Hz), 4.90 (1H, br s, OH), 6.49 (1H, d, J=8.0 Hz), 6.63 (1H, d, J=8.0 Hz).

IR (KBr)

ν 3376, 3082, 1611, 1502, 1460, 1379, 1332, 1245, 1122, 1038, 944, 868, 803 cm^{-1}.

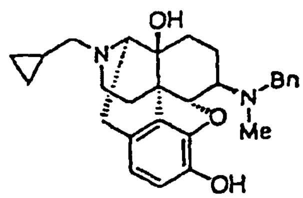
Mass (EI)

m/z 356 (M+).

[Reference Example 23]

6β-(N-Benzyl)methylamino-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxymorphinan 8

[0086]



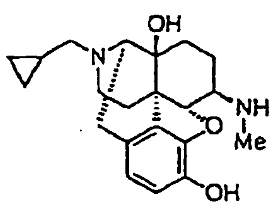
8

[0087] 50.08 g (0.108 mol) of naltrexone benzoate was suspended in THF (350 ml) followed by the addition of 19.61 g (0.162 mol) of benzylmethylamine. A Soxhlet extractor containing molecular sieves 4A (50 g) was attached followed by refluxing for 23 hours while heating. After adding methanol (200 ml) to the reaction system, 10.2 g (0.162 mol) of sodium cyanoborohydride was dissolved in methanol (50 ml) and added to the reaction mixture followed by stirring for 30 minutes. After stirring, the solvent was distilled off and ethylacetate (400 ml) and 1% aqueous sodium bicarbonate (400 ml) were added to the residue to separate layers. The aqueous layer was re-extracted with ethylacetate (80 ml). The resulting organic layer was washed with saturated brine (250 ml) and concentrated after drying. Methanol (240 ml) was added to the resulting residue to recrystallize and obtain 42.68 g of the target substance (yield: 88%). The data of this compound is the same as that shown in reference example 21.

[Reference Example 24]

17-Cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10 • phthalate

[0088]



10

[0089] 42.58 g (0.0953 mol) of 6β-(N-benzyl)methylamino-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxymorphinan 8 and 17.42 g (0.105 mol) of phthalic acid were dissolved in 500 ml of methanol followed by the addition of 12.7 g of 10% palladium-carbon and stirring for 12 hours in a hydrogen atmosphere. After the atmospheric hydrogen was replaced to nitrogen, 300 ml of methanol was added followed by refluxing while heating. After dissolving the precipitated crystals, the catalyst was filtered out during heating using Celite. After distilling off 200 ml of filtrate by atmospheric pressure condensation, the remaining filtrate was allowed to stand undisturbed to recrystallize and obtain 26.82 g of the target compound (yield: 54%).
mp 151-164°C (decomposition)
NMR (400 MHz, D20)

δ 0.40-0.50 (2H, m), 0.73 (1H, m), 0.82 (1H, m), 1.08 (1H, m), 1.56 (1H, m), 1.67 (1H, m), 1.85 (1H, m), 1.89-2.02

(2H, m), 2.52 (1H, ddd, J=13.2, 13.2, 4.9 Hz), 2.75 (1H, ddd, J=12.9, 12.9, 4.2 Hz), 2.78 (3H, s), 2.93-3.04 (2H, m), 3.16-3.25 (2H, m), 3.32-3.43 (2H, m), 4.07 (1H, br d, J=5.9 Hz), 4.99 (1H, d, J=7.3 Hz), 6.85 (1H, d, J=8.0 Hz), 6.90 (1H, d, J=8.0 Hz), 7.34-7.39 (2H, m), 7.43-7.48 (2H, m).

IR (KBr)

ν 3388, 3032, 1605, 1557, 1510, 1460, 1367, 1330, 1243, 1168, 1120, 1035, 992, 936, 859, 770 cm^{-1}.

Mass (FAB)

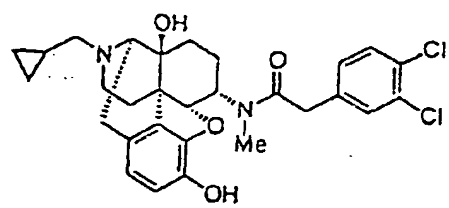
m/z 357 ((M+H)+).

Elementary Analysis: As $C_{21}H_{28}N_2O_3 \cdot C_8H_6O_4 \cdot 0.8H_2O$			
Calcd.:	C, 64.86;	H, 6.68;	N, 5.22.
Found.:	C, 64.93;	H, 6.61;	N, 5.23.

[Reference Example 25]

17-Cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3,4-dichlorophenylacetoamido)morphinan • hydrochloride 1

[0090]



1

[0091] 8.9 g of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 obtained in example 1 was dissolved in 180 ml of chloroform. After adding 10.4 ml of triethylamine, 10.4 ml of 3,4-dichlorophenylacetyl chloride (obtained by converting commercially available carboxylic acid into an acid chloride by established methods) was added dropwise at 0°C. After completion of dropwise addition, the reaction solution was stirred for 1 hour at room temperature followed by the addition of 150 ml of saturated aqueous sodium bicarbonate to the reaction system to separate. The aqueous layer was then extracted twice with 100 ml of chloroform. After drying with anhydrous sodium sulfate, the organic layer was concentrated. The resulting residue was dissolved in a mixed solvent of 140 ml of methanol and 14 ml of chloroform followed by the addition of 1.7 g of potassium carbonate at room temperature and Stirring for 30 minutes. 100 ml of water and 350 ml of chloroform were then added to the reaction solution to separate layers, and the aqueous layer was extracted twice with 80 ml of chloroform. After drying with anhydrous sodium sulfate, the resulting organic layer was concentrated. The resulting residue was recrystallized from a 2:1 mixture of ethylacetate and methanol to obtain 8.15 g of the free base form. This was then dissolved in a mixed solvent of chloroform and methanol followed by concentration after adjusting to pH 3 by addition of methanol solution of hydrochloride. This solution was reprecipitated from chloroform, methanol and ether to obtain 8.44 g of the target compound (yield: 58%).
mp 252-254°C
NMR (400 MHz, $DMSO-d_6$)

δ 0.43 (2H, m), 0.65 (2H, m), 1.05 (1H, m), 1.16 (1.5H, m), 1.37 (1H, m), 1.58 (2H, m), 1.92 (1H, m), 2.43 (1H, m), 2.68 (1H, m), 2.81 (0.5H, s), 2.96 (2.5H, s), 3.05 (2.5H, m), 3.30 (2H, m), 3.85 (3H, m), 4.48 (0.2H, m), 4.62 (0.8H, d, J=3.9 Hz), 4.75 (0.2H, m), 4.96 (0.8H, m), 6.21 (0.8H, m), 6.46 (0.2H, m), 6.58 (1H, d, J=8.3 Hz), 6.72 (1H, d, J=8.3 Hz), 7.25 (1H, m), 7.55 (2H, m), 8.80 (1H, brs), 9.32 (1H, brs)

IR (KRr)

ν 3370, 1620, 1510, 1473, 1120, 1035, cm^{-1}.

Mass (FAB)

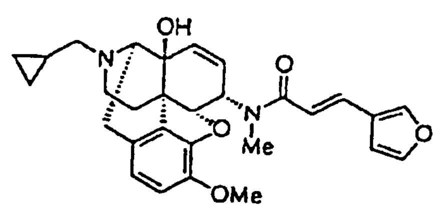
m/z 543 (M+H)+

Elementary Analysis: As $C_{29}H_{32}N_2O_4Cl_2 \cdot HCl \cdot 0.5H_20$				
Calcd.:	C, 59.14;	H, 5.82;	N, 4.75;	Cl, 18.06
Found.:	C, 59.34;	H, 5.78;	N, 4.78;	Cl, 17.78

[Reference Example 26]

17-Cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-14β-hydroxy-3-methoxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido] morphinan 75

[0092]



[0093] 540 mg of 17-cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-14β-hydroxy-3-methoxy-6α-(N-methyl-amino)morphinan 14 and 0.31 ml of triethylamine was dissolved in 10 ml of chloroform followed by addition of 250 mg of trans-3-(3-furyl)acryloyl chloride and stirring for 30 minutes at room temperature. The resulting solution was neutralized by addition of saturated aqueous sodium bicarbonate followed by extraction with chloroform. The organic layer was washed with saturated brine, dried and concentrated. The resulting residue was separated and purified by column chromatography (silica gel; chloroform~chloroform:methanol (100:1)] to obtain 610 mg of crude crystal. This was then recrystallized from dichloromethane-ether to obtain 580 mg of the target compound (yield: 81%).
mp 199-201°C
NMR (400 MHz, $CDCl_3$)

δ 0.19 (2H, m) 0.60 (2H, m), 0.93 (1H, m), 1.58 (1H, m), 1.74 (1H, m), 2.27-2.64 (4H, m), 2.78 (1H, m), 3.00 (3H, s), 3.09 (1H, d, J=18.6 Hz), 3.40 (1H, m), 3.82 (3H, s), 4.97 (1H, br s, OH), 5.14 (1H, d, J=6.8 Hz), 5.70-5.77 (2H, m), 5.83 (1H, m), 6.56 (1H, d, J=8.3 HZ), 6.61 (1H, d, J=1.5 Hz), 6.66 (1H, d, J=15.3 Hz), 6.67 (1H, d, J=8.3 Hz), 7.42 (1H, br s), 7.63 (1H, d, J=15.3 Hz), 7.65 (1H, br s).

IR (KBr)

ν 3338, 1659, 1638, 1404, 1282, 1205, 1160, 1122, 1054, 1017, 980, 808 cm^{-1}.

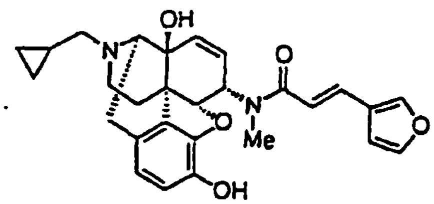
Mass (EI)

m/z 488 (M+).

[Reference Example 27]

17-Cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido] morphinan • hydrochloride 76

[0094]



76

[0095] 300 mg of 17-cyclopropylmethyl-7,8-didehydro-4,5α-epoxy-14β-hydroxy-3-methoxy-6α-[N-methyl-trans-3-(3-furyl)acrylamido] morphinan 75 was dissolved in 5 ml of anhydrous dichloromethane and cooled to 0°C. 3.7 ml of a dichloromethane solution of boron tribromide (1.0 M) was then added followed by stirring for 2 hours (at room temperature.). The reaction solution was cooled to 0°C followed by addition of 6 ml of 28% aqueous ammonia:water (1:4). After stirring for 30 minutes at 0°C, the reaction solution was extracted with chloroform and methanol (3:1). The organic layer was washed with saturated brine, dried and concentrated, and the resulting residue was purified with column chromatography [silica gel; chloroform~ chloroform:methanol:28% aqueous ammonia (100:2:0.2)] to obtain 350 mg of crude crystal. This was then recrystallized from dichloromethane, methanol and ethyl acetate to obtain 265 mg of a free base of the target compound. 238 mg of the resulting crystal was dissolved in 5 ml of methanol and concentrated after adding of an excess amount of methanol solution of hydrochloride. The residue was recrystallized from methanol to obtain 159.3 mg of the target compound (yield: 57%).
mp 251°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.43 (1H, m), 0.53 (1H, m), 0.62 (1H, m), 0.72 (1H, m), 1.07 (1H, m), 1.69-1.82 (1H, m), 2.54-3.02 (4H, m), 2.91 (3H, s), 3.08-3.18 (1H, m), 3.30-3.44 (2H, m), 4.07 (0.3H, m), 4.12 (0.7H, m), 4.94 (0.7H, d, J=6.8 Hz), 5.21 (0.3H, d, J=7.3 Hz), 5.49 (0.7H, m), 5.76 (0.3H, m), 5.83-5.94 (2H, m), 6.52-6.57 (1H, m), 6.69-6.76 (1.6H, m), 6.95 (0.7H, d, J=15.3 Hz), 7.05 (0.7H, d, J=2.0 Hz), 7.31 (0.3H, br s, OH), 7.46 (0.7H, br s, OH), 7.51 (1H, d, J=15.3 Hz), 7.70 (0.3H, br s), 7.74 (0.7H, br s), 8.09 (1H, br s), 8.90-9.06 (1H, m, NH+), 9.33 (0.3H, br s, OH), 9.34 (0.7H, br s, OH).

IR (KBr)

ν 3422, 3190, 1653, 1600, 1504, 1473, 1406, 1321, 1160, 1118, 1023, 949, 870, 799 cm^{-1}.

Mass (FAB)

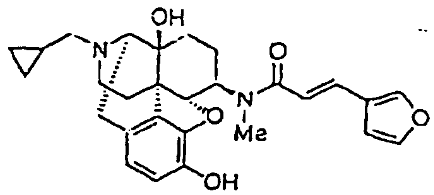
m/z 475 ((M+H)+).

Elementary Analysis: As $C_{28}H_{30}N_2O_5$ • HCl				
Calcd.:	C, 65.81;	H, 6.11;	Cl, 6.94;	N, 5.48.
Found.:	C, 65.62;	H, 6.19;	Cl, 6.82;	N, 5.61.

[Reference Example 28]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan. hydrochloride 78

[0096]



78

[0097] 21.12 g (0 0404 mol) of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methylamino)morphinan • phthalate 10 was dissolved in 110 ml of water. After adding 110 ml of THF and 8.75 g (0.0808 mol) of sodium carbonate, the atmosphere of reaction system was replaced to argon. Then, 6.96 g of trans-3-(3-furyl)acryloyl chloride (0.04444 mol) was dissolved in 40 ml of THF and added dropwise. After stirring for 30 minutes, 40 ml of methanol and 54 ml of 3 N aqueous sodium hydroxide were added and stirred for 1 hour. 350 ml of ethyl acetate and 250 ml of saturated aqueous sodium bicarbonate were added to the reaction solution to separate, and the aqueous layer was re-extracted with 100 ml of ethyl acetate. After washing with 200 ml of saturated brine, the resulting organic layer was dried with sodium sulfate and concentrated. The residue was dissolved in 630 ml of ethyl acetate while heating, and after dissolving, 150 ml was distilled off while heating. The resulting solution was allowed to stand and recrystallized to obtain 15.47 g of the free base of the target compound. 9.03 g of this free base was suspended in 90 ml of ethanol. After then adding 18.7 ml of 1 N aqueous hydrochloric acid, the resulting solution was concentrated and dried to obtain 9.72 g of the target compound (yield: 80%).
mp 187°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.42 (1H, m), 0.51 (1H, m), 0.60 (1H, m), 0.68 (1H, m), 1.07 (1H, m), 1.26 (0.4H, m), 1.32-1.50 (3.6H, m), 1.73 (1H, br d, J=13.7 Hz), 2.13 (1H, m), 2.40-2.60 (3H, m), 2.88 (1H, m), 2.92 (1.8H, s), 3.06 (1H, br d, J=13.18 Hz), 3.16 (1.2H, s), 3.59 (0.6H, m), 3.86 (1H, m), 4.19 (0.4H, m), 4.86 (0.6H, d, J=7.8 Hz), 4.92 (0.4H, d, J=7.8 Hz), 6.35 (0.6H, d, J=15.6 Hz), 6.40 (0.4H, br s), 6.50 (0.6H, br s), 6.62 (0.6H, s), 6.64 (0.4H, d, J=8.3 Hz), 6.71 (1H, d, J=8.3 Hz), 6.85 (0.6H, d, J=8.3 Hz), 6.90 (0.4H, d, J=15.1 Hz), 6.99 (0.4H, s), 7.22 (0.6H, d, J=15.6 Hz), 7.36 (0.4H, d, J=15.1 Hz), 7.66 (0.6H, s), 7.72 (0.4H, s), 7.92 (0.6H, s), 8.03 (0.4H, s), 8.85 (1H, br s), 9.28 (0.4H, s), 9.68 (0.6H, s)

IR (KBr)

ν 3376, 1653, 1506, 1599, 1410, 1323, 1158, 1127, 1033, 872, 799 cm^{-1}.

Mass (FAB)

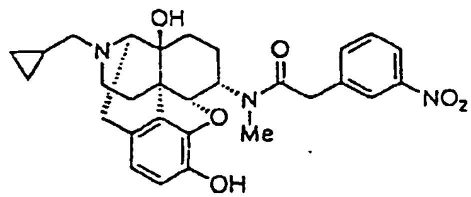
m/z 477 (M+H)

Elementary Analysis: As $C_{28}H_{32}N_2O_5$ • HCl • $0.2H_20$				
Calcd.:	C, 65.10;	H, 6.52;	N, 5.42;	Cl, 6.86.
Found.:	C, 65.11;	H, 6.63;	N, 5.60;	Cl, 6.80.

[Reference Example 29]

17-Cyclopropylmethyl-3,14-β-dihydroxy-4,5α-epoxy-6α-(N-methyl-3-nitrophenylacetamido)morphinan • hydrochloride 83

[0098]



83

[0099] 567.1 mg (1.59 mmol) of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-methylaminomorphinan 4 and 577.9 mg (3.19 mol) of 3-nitrophenylacetic acid were dissolved in 18 ml of chloroform followed by the addition of 657.0 mg (3.18 mmol) of dicyclohexylcarbodiimide and 10.0 mg (0.082 mmol) of 4-(N,N-dimethylamino)pyridine to this solution and stirring for 1 hour at room temperature. The solid that formed in the reaction solution was filtered out, the residue was washed with chloroform, and the filtrate and washing were combined and concentrated. The resulting solid was dissolved in a mixed solution of methanol and chloroform (4:1) followed by the addition of 445 mg (3.22 mmol) of potassium carbonate and stirring for 2 hours at room temperature. 15 ml of water was added to the reaction solution followed by extraction with chloroform (3 x 15 ml). The organic layers were then combined and concentrated to obtain 2.27 g of solid. This solid was then purified with column chromatography [silica gel 80 g; chloroform-methanol (40:1→20:1)] to obtain 717.4 mg of the free base of the target compound (yield: 87%). This crystal was then dissolved in methanol followed by addition of methanol solution saturated with hydrogen chloride gas. The precipitated crystal was then filtered to obtain 300.5 mg of the target compound (yield: 34%). In addition, the crystal resulting from concentration of this filtrate was then recrystallized from methanol to further obtain 354.0 mg of the target compound (yield: 40%). Both of these compounds were then combined to obtain 654.5 mg of the target compound (yield: 74%).
mp >210°C (decomposition, methanol)
NMR (400 MHz, DMSO-d_6)

δ 0.39 (1H, m), 0.47 (1H, m), 0.61 (1H, m), 0.68 (1H, m), 1.06 (1H, m), 1.17 (1H, m), 1.37 (1H, m), 1.50-1.64 (2H, m), 1.94 (1H, m), 2.43 (1H, m), 2.68 (1H, m), 2.82 (0.6H, s), 2.90-3.14 (3H, m), 3.00 (2.4H, s), 3.22-3.38 (2H, m), 3.90-4.10 (3H, m), 4.54 (0.2H, m), 4.63 (0.8H, d, J=3.3 Hz), 4.82 (0.2H, m), 4.98 (0.8H, m), 6.28 (1H, br s, OH), 6.58 (1H, d, J=7.8 Hz), 6.75 (1H, d, J=7.8 Hz), 7.62 (0.8H, dd, J=7.8, 7.8 Hz), 7.65 (0.2H, dd, J=7.8, 7.8 Hz), 7.71 (0.8H, d, J=7.8 Hz), 7.75 (0.2H, d, J=7.8 Hz), 8.13 (1H, d, J=7.8 Hz), 8.14 (1H, br s), 8.84 (1H, m, NH+), 9.36 (1H, s, OH).

IR (KBr)

ν 3388, 1618, 1528, 1466, 1352, 1321, 1120, 1036, 920, 806 cm^{-1}.

Mass (FAB)

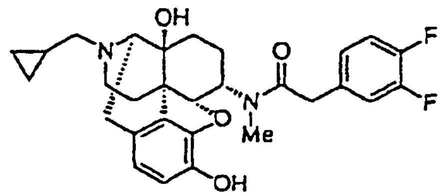
m/z 520 ((M+H)+).

Elementary Analysis: As $C_{29}H_{33}N_3O_6$ • HCl				
Calcd.:	C, 62.64;	H, 6.16;	N, 7.56;	Cl, 6.38.
Found.:	C, 62.25;	H, 6.39;	N, 7.68;	Cl, 6.20.

[Reference Example 30]

17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(N-methyl-3,4-difluorophenylacetamido)morphinan • hydrochloride 105

[0100]



105

[0101] 128 mg of 3,4-difluorophenylacetic acid and 131 mg of carbonyl diimidazole were dissolved in 2.5 ml of anhydrous tetrahydrofuran. After refluxing while heating for 30 minutes, the solution was cooled to room temperature. A solution of 200 mg of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 dissolved in 13 ml of anhydrous tetrahydrofuran was added to the reaction solution followed by refluxing while heating for 1 hour. After cooling to room temperature, the reaction solution was concentrated and the resulting residue was dissolved in 16 ml of methanol and stirred for 1 hour following the addition of 1 ml of 1 N aqueous sodium hydroxide. The reaction system was then concentrated followed by the addition of 40 ml of ethylacetate to the residue and sequential washing with 25 ml of water and 25 ml of saturated brine. After drying with anhydrous sodium sulfate, the organic layer was concentrated to obtain 439 mg of crude product. This was then recrystallized from ethylacetate to obtain 190 mg of the free base of the target compound. The mother liquor was then purified with silica gel column chromatography (25 g chloroform/methanol = 19/1) to obtain 177 mg of the free base of the target compound. The free base obtained in this manner was then dissolved in a mixed solvent of chloroform and methanol, and this solution was concentrated after adding methanol solution of hydrochloride to adjust to pH 4. The residue was re-precipitated with ether and filtered to obtain 176 mg of the target compound (yield: 57%).
mp 194-208°C (decomposition, diethylether)
NMR (400 MHz, DMSO-d_6)

δ 0.31-0.43 (1H, m), 0.43-0.53 (1H, m), 0.53-0.64 (1H, m), 0.64-0.76 (1H, m), 0.99-1.12 (1H, m), 1.12-1.28 (1H, m), 1.28-1.45 (1H, m), 1.45-1.67 (2H, m), 1.86-2.03 (1H, m), 2.35-2.50 (1H, m), 2.59-2.77 (1H, m), 2.80 (0.6H, s), 2.88-3.18 (3H, m), 2.96 (2.4H, s), 3.18-3.39 (2H, m), 3.78 (1.6H, s), 3.88 (0.4H, s), 3.91 (1H, d, J=6.8 Hz), 4.49 (0.2H, m), 4.62 (1H, d, J=3.4 Hz), 4.97 (0.8H, dt, J=14.2, 3.4 Hz), 6.25 (0.8H, br s), 6.56 (0.2H, br s), 6.58 (1H, d, J=7.8 Hz), 6.73 (1H, d, J=7.8 Hz), 7.03-7.18 (1H, m), 7.25-7.45 (2H, m), 8.82 (1H, br s), 9.32 (1H, s)

IR (KBr)

ν 1620, 1560, 1520, 1460, 1278, 1172, 1120, 1036, 774 cm^{-1}.

Mass (FAB)

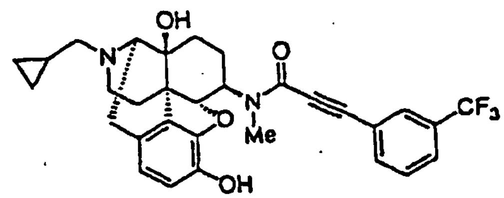
m/z 511 ((M+H)+).

Elementary Analysis: As $C_{29}H_{33}N_2O_4ClF_2 \cdot 0.7H_2O \cdot 0.25AcOEt$					
Calcd.:	C, 61.95;	H, 6.31;	N, 4.82;	Cl, 6.09;	F, 6.53
Found.:	C, 61.91;	H, 6.47;	N, 4.81;	Cl, 6.04;	F, 6.53

[Reference Example 31]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-(3-trifluoromethylphenyl)propiolamido] morphinan • hydrochloride 124

[0102]



124

[0103] 400 mg (1.12 mmol) of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10 and 360 mg (1.68 mmol) of 3-(3-trifluoromethylphenyl)propiolic acid were dissolved in 12 ml of chloroform followed by sequential addition of 0.40 ml (2.91 mmol) of N-ethylpiperidine and 428 mg (1.68 mmol) of bis-(2-oxo-3-oxazolidinyl)phosphinic chloride and stirring for 12 hours at room temperature. Then, 15 ml of 1 N aqueous sodium hydroxide were added to separate layers, and the organic layer was washed with 10 ml each of water and saturated brine, dried and concentrated. The residue was dissolved in 10 ml of methanol followed by the addition of 2ml of 1 N aqueous sodium hydroxide and stirring for 3 hours. 30 ml of ethylacetate were then added to separate layers, and the resulting organic layer was washed with 20 ml of saturated brine, dried and concentrated. The residue was purified with silica gel column chromatography (Merk 9385, 30 g, chloroform/methanol = 30/1) to obtain 562.8 mg of the free base of the target compound. This was then re-precipitated from hexane and ethylacetate, and the resulting solid was dissolved in ethylacetate. An excess amount of ethylacetate solution of hydrochloride solution was added followed by stirring and filtration of the resulting precipitate to obtain 274 mg of the target compound (yield: 42%).
mp >195°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.42 (1H, m), 0.52 (1H, m), 0.59 (1H, m), 0.67 (1H, m), 1.07 (1H, m), 1.29-1.51 (3H, m), 1.73-1.83 (1H, m), 2.09-2.26 (1H, m), 2.40-2.58 (2H, m), 2.86 (1H, m), 2.98 (2.4H, s), 3.02-3.11 (2H, m), 3.31 (0.6H, s), 3.30-3.38 (2H, m), 3.87 (1H, br d, J=5.9 Hz), 4.13 (1H, m), 4.89 (0.8H, d, J=8.3 Hz), 4.96 (0.2H, d, J=8.3 Hz), 6.40 (0.2H, s, OH), 6.46 (0.8H, d, J=7.3 Hz), 6.53 (0.8H, s, OH), 6.60 (0.8H, d, J=7.3 Hz), 6.66 (0.2H, d, J=7.3 Hz), 6.72 (0.2H, d, J=7.3 Hz), 7.47 (0.8H, br s), 7.57 (0.8H, d, J=7.8 Hz), 7.63 (0.8H, dd, J=7.8, 7.8 Hz), 7.73 (0.2H, dd, J=7.8, 7.8 Hz),7.83 (0.8H, d, J=7.8 Hz), 7.90 (0.2H, d, J=7.8 Hz), 7.97 (0.2H, d, J=7.8 Hz), 8.06 (0.2H, br s), 8.81 (1H, m, NH+), 9.30 (0.8H, s, OH), 9.31 (0.2H, s, OH).

IR (KBr)

ν 3400, 2224, 1620, 1439, 1334, 1170, 1127, 1073, 1035, 924, 806 cm^{-1}.

Mass (FAB)

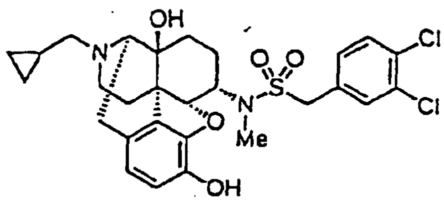
m/z 553 ((M+H)+).

Elementary Analysis: As $C_{31}H_{31}F_3N_2O_4$ • HCl • $0.5H_20$					
Calcd.:	C, 62.26;	H, 5.56;	Cl, 5.93;	F, 9.53;	N, 4.68
Found.:	C, 62.25;	H, 5.64;	Cl, 5.78;	F, 9.49;	N, 4.73

[Reference Example 32]

17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3,4-dichlorophenylmethanesulfonamido) morphinan • tartrate 128

[0104]



128

[0105] 227 mg of 3-tert-butyldimethylsilyloxy-17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-6α-(N-methyl-3,4-dichlorophenylmethanesulfonamido)morphinan 16 obtained in reference example 8 was dissolved in 4.5 ml of tetrahydrofuran followed by the addition of 0.39 ml of tetrabutylammonium fluoride and stirring for 30 minutes. 15 ml of ethylacetate and 10 ml of saturated aqueous ammonium chloride were added to separate layers, and the aqueous layer was extracted twice with 10 ml of ethylacetate. The resulting organic layer was concentrated after drying with anhydrous sodium sulfate, and the residue was purified with silica gel column chromatography (25 g chloroform/methanol = 20/1) to obtain the crude compound. This was then recrystallized from ethylacetate and methanol to obtain 158 mg of the free base of the target compound. This was dissolved in a mixed solvent of chloroform and methanol, completely dissolved by addition of 20.4 mg of tartaric acid and concentrated. This residue was re-precipitated from methanol and ether followed by filtration to obtain 105 mg of the target compound (yield: 49%).
mp >149°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.13-0.22 (2H, m), 0.47-0.58 (2H, m), 0.82-0.92 (1H, m), 0.98-1.11 (1H, m), 1.18-1.27 (1H, m), 1.35-1.48 (2H, m), 1.55-1.67 (1H, m), 2.07-2.26 (2H, m), 2.48-2.60 (1H, m), 2.60-2.73 (2H, m), 2.83 (3H, s), 3.01 (1H, brd, J=8.6 Hz), 2.90-4.00 (5H, m, 3 × OH), 3.98-4.07 (1H, m), 4.11 (1H, s), 4.35 (1H, d, J=3.4 Hz), 4.49 (1H, d, J=13.7 Hz), 4.53 (1H, d, J=13.7 Hz), 6.49 (1H, d, J=8.3 Hz), 6.61 (1H, d, J=8.3 Hz), 7.44 (1H, dd, J=2.0, 8.3 Hz), 7.67 (1H, d, J=8.3 Hz), 7.71 (1H, d, J=2.0 Hz), 9.08 (1H, brs).

IR (KBr)

ν 3410, 1607, 1470, 1323, 1122, 1035, 959, 917 cm^{-1}.

Mass (FAB)

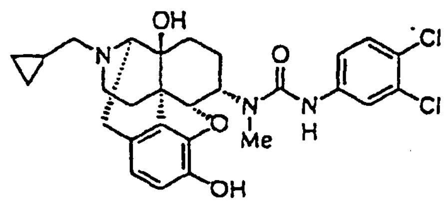
m/z 579 (M+H)+.

Elementary Analysis: As $C_{28}H_{32}N_2O_5Cl_2S \cdot 0.65C_4H_6N_6 \cdot 0.4H_20$					
Calcd.:	C, 53.71;	H, 5.41;	N, 4.09;	Cl, 10.36;	S, 4.69
Found.:	C, 53.79;	H, 5.50;	N, 4.12;	Cl, 10.09;	S, 4.58

[Reference Example 33]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[N-methyl-N'-(3,4-dichlorophenyl)ureido]morphinan • hydrochloride 131

[0106]



131

[0107] 17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-methylaminomorphinan 4 (0.20 g) was dissolved in chloroform (5 ml) followed by the addition of 3,4-dichlorophenylisocyanate (0.26 g, 2.5 equivalents) and reacting for 5 minutes at room temperature. The precipitated solid was filtered out and dissolved in chloroform (8 ml) and methanol (10 ml) followed by the addition of 3 N aqueous sodium hydroxide to carry out hydrolysis for 5 minutes at room temperature. The solvent was distilled off followed by addition of saturated aqueous sodium bicarbonate (10 ml) and distilled water (4 ml), extraction with chloroform and methanol (12/2 + 10/2 ml), and drying with anhydrous sodium sulfate. After purifying with silica gel column chromatography (Merk 9385, 20 g; chloroform → 3% methanol/chloroform), the residue was again dissolved in chloroform and methanol (5/0.5 ml) followed by addition of methanol solution of hydrochloric acid to obtain the target compound (0.23 g, 70%) in the form of its hydrochloride.
mp 210°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.41 (1H, m), 0.44 (1H, m), 0.62 (1H, m), 0.68 (1H, m), 1.0-1.2 (2H, m), 1.40 (1H, m), 1.60 (2H, m), 1.94 (1H, m), 2.4-2.5 (1H, m), 2.68 (1H, m), 2.92 (3H, s), 2.9-3.2 (3H, m), 3.3-3.4 (2H, m), 3.91 (1H, d, J=6.8 Hz), 4.74 (1H, d, J=3.9 Hz), 4.81 (1H, dt, J=13.7, 3.9 Hz), 6.34 (1H, s), 6.59 (1H, d, J=7.8 Hz), 6.73 (1H, d, J=7.8 Hz), 7.49 (1H, d, J=8.8 Hz), 7.55 (1H, dd, J=9.3, 2.4 Hz), 7.94 (1H, d, J=2.4 Hz), 8.73 (1H, s), 8.82 (1H, brs), 9.32 (1H, s)

IR (KBr)

ν 3300, 1638, 1510, 1477, 1120, 1040 cm^{-1}.

Mass (FAB)

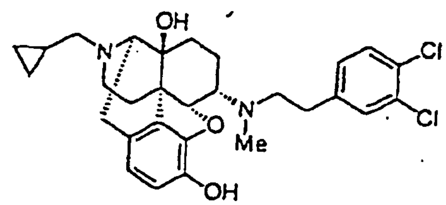
m/z 544 (M+H)

Elementary Analysis: As $C_{28}H_{31}N_3O_4Cl_2$ • HCl • $0.4H_20$				
Calcd.:	C 57.18;	H 5.62;	N 7.14;	Cl 18.08
Found.:	C 57.32;	H 5.83;	N 7.04;	Cl 17.85

[Reference Example 34]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-[N-methyl-N-2-(3,4-dichlorophenyl)ethylamino]morphinan • 1.8 hydrochloride 135

[0108]



135

[0109] 234.5 mg (0.431 mmol) of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(N-methyl-3,4-dichlorophenylacetamido)morphinan (free base of 1) was dissolved in 5.0 ml of anhydrous THF under argon atmosphere followed by the dropwise addition of 1.1 ml (2.2 mmol) of a 2.0 M anhydrous THF solution of borane-dimethylsulfide complex at 0°C and refluxing for 1.5 hours. This reaction solution was cooled to 0°C followed by the addition of 2 ml of 6 N hydrochloric acid and again refluxing for 1 hour. The reaction solution was again cooled to 0°C and 25 ml of saturated aqueous sodium bicarbonate was added to make the solution basic. The solution was then extracted with chloroform and methanol (4:1) (3 x 20 ml), and the organic layers were combined, dried and concentrated to obtain 281 mg of an oily substance. This oily substance was purified with column chromatography [silica gel 25 g; chloroform-methanol (50:1→40:1)] to obtain 191.0 mg of the free base of the target compound. This free base was dissolved in methanol followed by the addition of a methanol solution of hydrogen chloride and concentration. The resulting hydrochloride was purified with Sephadex gel column chromatography [methanol] to obtain 193.3 mg of the target compound (yield: 74%).
mp >205°C (decomposition)
NMR (400 MHz, $CDCl_3$; data for free base)

δ 0.13 (2H, m), 0.53 (2H, m), 0.85 (1H, m), 1.00 (1H, m), 1.49 (1H, dd, J=15.1, 8.8 Hz), 1.53-1.62 (2H, m), 1.71 (1H, ddd, J=15.1, 9.5, 9.5 Hz), 2.0-3.1 (1H, br s, OH), 2.15-2.40 (4H, m), 2.51 (3H, s), 2.55-2.67 (2H, m), 2.72-2.85 (3H, m), 2.89 (1H, m), 2.98-3.10 (3H, m), 4.78 (1H, dd, J=3.0, 2.0 Hz), 4.98 (1H, br s, OH), 6.50 (1H, d, J=8.1 Hz), 6.68 (1H, d, J=8.1 Hz), 7.03 (1H, dd, J=8.3, 2.0 Hz), 7.28 (1H, d, J=2.0 Hz), 7.33 (1H, d, J=8.3 Hz).

IR (KBr)

ν 3422, 1638, 1620, 1508, 1470, 1390, 1323, 1241, 1172, 1122, 1035, 982, 919, 886 cm^{-1}.

Mass (FAB)

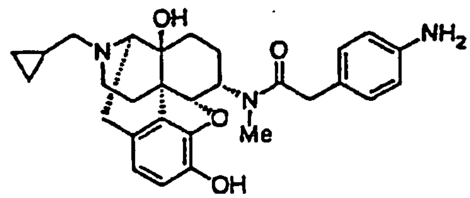
m/z 529 ((M+H)+).

Elementary Analysis: As $C_{29}H_{34}Cl_2N_2O_3 \cdot 1.8HCl \cdot 0.4H_2O$				
Calcd.:	C, 57.83;	H, 6.12;	N, 4.65;	Cl, 22.37
Found.:	C, 57.73;	H, 6.31;	N, 4.60;	Cl, 22.38

[Reference Example 35]

17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(N-methyl-4-aminophenylacetamido)morphinanan • 1.6 hydrochloride 137

[0110]



137

[0111] 156.8 mg (0.282 mmol) of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(N-methyl-4-nitrophenylacetamido) morphinan • hydrochloride 87 was dissolved in 2.1 ml of methanol followed by the addition of roughly 0.2 ml of a saturated methanol solution of hydrogen chloride gas and 5.3 mg of platinum oxide, and stirring for 2.5 hours at room temperature in a hydrogen atmosphere (1 atm). The reaction mixture was filtered by passing through Celite, and the filtration residue was washed with methanol. The filtrate and washing were combined and concentrated to obtain 166 mg of crude product. This crude product was purified twice with Sephadex column chromatography [methanol] to obtain 108.2 mg of the target compound (yield: 68%).
mp >220°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.39 (1H, m), 0.47 (1H, m), 0.62 (1H, m), 0.69 (1H, m), 1.00-1.23 (2H, m), 1.34 (1H, m), 1.45-1.63 (2H, m), 1.94 (1H, m), 2.44 (1H, m), 2.68 (1H, m), 2.78 (0.9H, s), 2.92-3.13 (3H, m), 2.93 (2.1H, s), 3.21-3.43 (2H, m), 3.67-3.82 (2H, m), 3.92-3.98 (1H, m), 4.38 (0.3H, m), 4.57 (0.3H, m), 4.61 (0.7H, d, J=3.4 Hz), 4.98 (0.7H, m), 6.29 (0.7H, br s, OH), 6.57 (1H, d, J=8.3 Hz), 6.63 (0.3H, br s, OH), 6.72 (0.3H, d, J=8.3 Hz), 6.74 (0.7H, d, J=8.3 Hz), 6.97 (0.6H, d, J=8.3 Hz) 7.00 (1.4H, d, J=8.3 Hz), 7.16 (1.4H, d, J=8.3 Hz), 7.20 (0.6H, d, J=8.3 Hz), 8.53 (2.8H, br s, NH3+), 8.84 (0.8H, m, NH+), 9.30 (0.3H, br s, OH), 9.33 (0.7H, br s, OH).

IR (KBr)

ν 3370, 1620, 1510, 1466, 1321, 1120, 1038, 919, 804 cm^{-1}.

Mass (FAB)

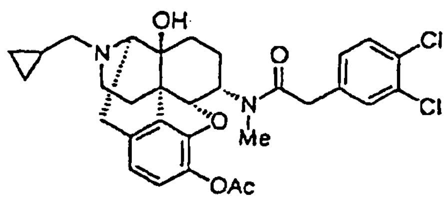
m/z 490 ((M+H)+).

Elementary Analysis: As $C_{29}H_{35}N_3O_4$ • 1.6HCl • $0.8H_20$				
Calcd.:	C, 61.94;	H, 6.85;	N, 7.47;	Cl, 10.09.
Found.:	C, 62.09;	H, 7.02;	N, 7.15;	Cl, 9.93.

[Reference Example 36]

17-Cyclopropylmethyl-3-acetoxy-4,5α-epoxy-14β-hydroxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan • hydrochloride 139

[0112]



139

[0113] 152 mg of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan • hydrochloride 1 obtained in reference example 25 was dissolved in 2.3 ml of pyridine followed by the addition of 0.04 ml of acetic anhydride and stirring for 30 minutes. After concentrating the reaction solvent and removing the pyridine by azeotrope with toluene, the residue was washed with ether to obtain 148 mg of the target compound (yield: 91%).
mp >187°C (decomposition)
NMR (400 MHz, $CDCl_3$)

δ 0.35-0.58 (1.3H, m), 0.63-0.94 (2.7H, m),1.25-1.75 (5H, m), 2.26 (2.1H, s), 2.27 (0.9H, s), 2.47-2.70 (2H, m), 2.83 (0.9H, s), 2.85 (2.1H, s), 2.90-3.26 (4H, m), 3.27-3.60 (2H, m), 3.69 (1.4H, s), 3.71 (0.6H, s), 4.35-4.60 (1.3H, m), 4.75-4.83 (0.3H, m), 4.86 (0.7H, d, J=2.9 Hz), 5.18-5.28 (0.7H, m), 6.70 (1H, d, J=8.4 Hz), 6.72 (1H, brs), 6.87-6.93 (1H, m), 7.09 (0.7H, dd, J=8.3, 2.0 Hz), 7.30 (0.3H, dd, J=8.3, 2.0 Hz), 7.35 (0.7H, d, J=2.0 Hz), 7.40 (0.7H, d, J=8.3 Hz), 7.48 (0.3H, d, J=2.0 Hz), 7.56 (0.3H, d, J=8.3 Hz), 9.40-9.70 (1H, m).

IR (KBr)

ν 3380, 1765, 1636, 1626, 1475, 1458, 1224, 1201, 1122, 1036 cm^{-1}.

Mass (FAB)

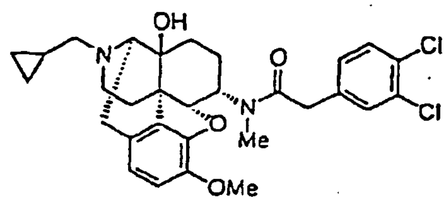
m/z 585 (M+H)+.

Elementary Analysis: As $C_{31}H_{34}N_2O_5Cl_2$ • HCl				
Calcd.:	C, 59.86;	H, 5.67;	N, 4.50;	Cl, 17.10
Found.:	C, 59.71;	H, 5.70;	N, 4.55;	Cl, 16.95

[Reference Example 37]

17-cyclopropylmethyl-4,5α-epoxy-14β-hydroxy-3-methoxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan • tartrate 142

[0114]



142

[0115] 245 mg of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan (free base of 1) obtained in reference example 25 was dissolved in 3.5 ml of chloroform followed by the addition of an excess amount of diazomethane and stirring for 1 hour. After concentrating the reaction system, the residue was purified with silica gel column chromatography (20 g hexane/ethylacetate/methanol/aqueous ammonia = 5/3/0.2/0.04) to obtain the free base of the target compound. After dissolving this in methanol, 11 mg of tartaric acid was added to completely dissolve followed by concentration. The residue was re-precipitated from ether followed by filtration to obtain 83 mg of the target compound (yield: 30%).
mp >115°C (decomposition)
NMR (400 MHz, DMSO-d_6 + D20)

δ 0.15-0.33 (2H, m), 0.48-0.63 (2H, m), 0.87-1.00 (1H, m), 1.05-1.55 (4H, m), 1.69-1.85 (1H, m), 2.20-2.45 (2H, m), 2.55-2.95 (3H, m), 2.79 (0.9H, s), 2.94 (2.1H, s), 3.08-3.22 (1H, m), 3.30-3.58 (2H, m), 3.78 (3H, s) 3.77 (1H, d, J=16.1 Hz), 3.84 (1H, d, J=16.1 Hz), 4.09 (2H, s), 4.38-4.45 (0.3H, m), 4.55-4.63 (0.3H, m), 4.60 (0.7H, d, J=3.4 Hz), 4.88-4.96 (0.7H, m), 6.68 (0.7H, d, J=8.3 Hz), 6.64-6.70 (0.3H, m), 6.86 (0.7H, d, J=8.3 Hz), 6.82-6.88 (0.3H, m), 7.24 (0.7H, dd, J=8.3, 2.0 Hz), 7.24-7.30 (0.3H, m), 7.52 (0.7H, d, J=2.0 Hz), 7.52-7.56 (0.3H, m), 7.57 (0.7H, d, J=8.3 Hz), 7.60 (0.3H, d, J=8.3 Hz).

IR (KBr)

ν 3324, 1628, 1402, 1309, 1267, 1131 cm^{-1}.

Mass (EI)

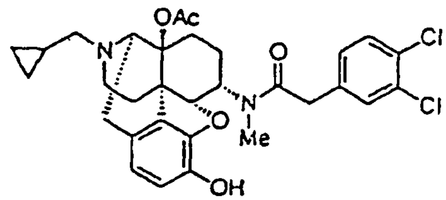
m/z=556 M+.

Elementary Analysis: As $C_{30}H_{34}N_2O_4Cl_2 \cdot 0.87C_4H_6O_6 \cdot 0.7H_2O$				
Calcd.:	C 57.39;	H 5.80;	N 4.00;	Cl 10.12
Found.:	C 57.35;	H 5.91;	N 4.09;	Cl 10.19

[Reference Example 38]

14β-Acetoxy-17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan • hydrochloride 143

[0116]



143

[0117] 443 mg of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3,4-dichlorophenylacetamido) morphinan (free base of 1) obtained in reference example 25 was dissolved in acetic anhydride followed by stirring for 1 hour at 160°C with an oil bath. After concentrating the reaction solvent, the acetic anhydride was completely removed by azeotrope with toluene. The residue was dissolved in 10 ml of methanol followed by the addition of 14 ml of 4% aqueous sulfuric acid and stirring for 18 hours. 10 ml of aqueous ammonia and 30 ml of chloroform were then added to the system to separate, and the aqueous layer was extracted twice with 15 ml of chloroform. The organic layer was concentrated after drying with anhydrous sodium sulfate and the residue was purified with silica gel column chromatography (45g, chloroform/ethylacetate = 2/1). This was then recrystallized from chloroform and methanol followed by derivation of the crystals into hydrochloride with methanol solution of hydrochloride to obtain 299 mg of the target compound (yield: 59%).
mp >190°C (decomposition)
NMR (400 MHz, DMSO-d_6)

δ 0.35-0.73 (4H, m), 0.90-1.03 (1H, m), 1.05-1.75 (4H, m), 2.17 (2.25H, s), 2.24 (0.75H, s),2.30-2.62 (2H, m), 2.65-2.83 (1H, m), 2.80 (0.75H, s), 2.96 (2.25H, s), 2.90-3.15 (2H, m), 3.18-3.52 (3H, m), 3.79 (0.75H, d, J=16.1 Hz), 3.84 (0.75H, d, J=16.1 Hz), 3.93-4.07 (0.5H, m), 4.55-4.60 (0.25H, m), 4.72 (0.75H, d, J=3.4 Hz), 4.77-4.85 (1H, m), 5.26 (1H, d, J=6.4 Hz), 6.50 (0.25H, d, J=8.3 Hz), 6.61 (0.75H, d, J=8.3 Hz), 6.77 (1H, d, J=8.3 Hz), 7.19-7.25 (0.25H, m), 7.24 (0.75H, dd, J=8.3, 2.0 Hz), 7.49 (0.25H, d, J=2.0 Hz), 7.52 (0.75H, d, J=2.0 Hz), 7.58 (0.75H, d, J=8.3 Hz), 7.60 (0.25H, d, J=8.3 Hz), 9.20-9.47 (1H, m), 9.42 (0.25H, s), 9.43 (0.75H, s).

IR (KBr)

ν 3420, 1744, 1626, 1473, 1406, 1371, 1321, 1214, 1116, 1035 cm^{-1}.

Mass (EI)

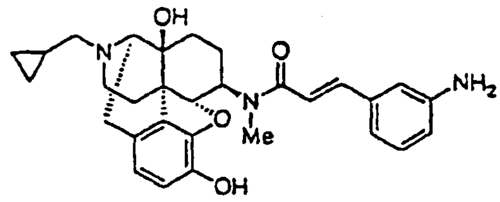
m/z 584 M+.

Elementary Analysis: As $C_{31}H_{34}N_2O_5Cl_2$ • HCl • 0.2$H_2$0				
Calcd.:	C, 59.52;	H, 5.70;	N, 4.48;	Cl, 17.00.
Found.:	C, 59.40;	H, 5.90;	N, 4.56;	Cl, 17.12.

[Reference Example 39]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(N-methyl-3-aminocinnamamido)morphinan • hydrochloride 145

[0118]



145

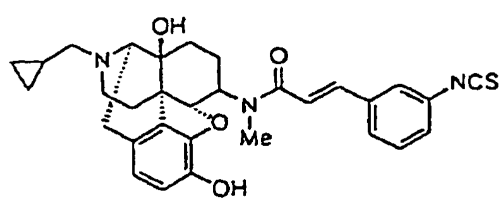
[0119] 360 mg of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(N-methyl-3-nitrocinnamamido)morphinan and 1.07 g of stannic chloride dihydrate was dissolved in 7.5 ml of ethanol followed by heating to 70°C and stirring for 2 hours. After cooling the reaction mixture to room temperature, 2 N aqueous sodium hydroxide was added while cooling with ice to neutralize followed by extraction with dichloromethane. The organic layers were combined and washed with saturated brine. After drying and concentrating, the organic substances were removed by chromatographic filtration [silica gel; chloroform:methanol (9:1)]. The resulting crude target compound was converted into a dihydrochloride to obtain 310 mg.
Mass (FAB)

m/z 502 ((M+H)+).

[Reference Example 40]

17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(N-methyl-3-isothiocyanatocinnamamido)morphinanan • methanesulfonate 146

[0120]



146

[0121] 300 mg of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-(N-methyl-3-aminocinnamamido)morphinan • hydrochloride 145 obtained in reference example 39 was dissolved in 9 ml of water and cooled with ice. 40 μl of thiophosgene dissolved in 2 ml of chloroform was added dropwise followed by stirring for 5 hours at warming to room temperature. Saturated aqueous sodium bicarbonate was then added to neutralize while cooling with ice followed by extraction with chloroform. The organic layers were combined and washed with saturated brine followed by drying and concentrating. The resulting residue was purified with column chromatography [silica gel; chloroform:methanol (97.5:2.5)], to obtain 208 mg of the resulting target compound after converting a methanesulfonate from (yield: 52% 2 steps).

mp 170°C (decomposition)
NMR (500 MHz, DMSO-d_6)

δ 0.42 (1H, m), 0.49 (1H, m), 0.60 (1H, m), 0.69 (1H, m), 1.07 (1H, m), 1.27-1.58 (3H, m), 1.72 (1H, m), 2.11 (1H, m), 2.31 (3H, s), 2.43-2.52 (2H, m), 2.86 (1H, m), 2.92 (2.1H, s), 3.02-3.14 (2H, m), 3.18 (0.9H, s), 3.30-3.38 (2H, m), 3.70 (0.7H, m), 3.83 (1H, m), 4.19 (0.3H, m), 4.80 (0.7H, d, J=8.3 Hz), 4.90 (0.3H, d, J=8.3 Hz), 6.14 (0.3H, br s), 6.22 (0.7H, br s), 6.65-6.84 (2.1H, m), 6.88 (0.7H, d, J=7.8 Hz), 7.29 (1H, d, J=15.6 Hz), 7.40-7.50 (3.6H, m), 7.69 (0.3H, d, J=7.8 Hz), 7.91 (0.3H, s), 8.74 (1H, br s), 9.30 (0.3H, br s), 9.54 (0.7H, br s).

IR (KBr)

ν 3380, 3210, 2124, 1649, 1599, 1197, 1060, 785 cm^{-1}.

Mass (FAB)

m/z 544 ((M+H)+).

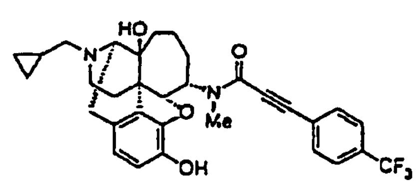
Elementary Analysis: As $C_{31}H_{33}N_3O_4S \cdot CH_3SO_3H \cdot H_20$				
Calcd.:	C, 58.43;	H, 5.98;	N, 6.39;	S, 9.75
Found.:	C, 58.67;	H, 6.15;	N, 6.11;	S, 9.78

[Examples 210-213]

[0122] The procedure of Reference Example 31 was repeated, except that 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-methylaminomorphinan and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-methylaminomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10 and 3-(4-trifluoromethylphenyl)propiolic acid was used instead of 3-(3-trifluoromethylphenyl)propiolic acid, thereby preparing 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan hydrochloride 222 (yield: 68%), 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-[N-methyl-3-(3-trifluoromethylphenyl)propiolamido]morphinan hydrochloride 223 (yield: 61%), 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6α-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan hydrochloride 224 (yield: 69%) and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-10-keto-6β-[N-methyl-3-(4-trifluoromethylphenyl)propiolamido]morphinan hydrochloride 225 (yield: 65%).

Compound 222

[0123]



222

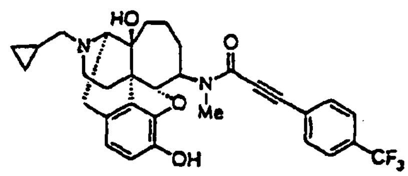
Mass (FAB)

m/z 567 ($(M+H)^+$).

Elementary analysis for $C_{32}H_{33}N_2O_4F_3 \cdot HCl \cdot 0.2H_2O$					
Calculated:	C, 63.35;	H, 5.71;	N, 4.62;	F, 9.39;	Cl, 5.84.
Found:	C, 63.25;	H, 5.75;	N, 4.72;	F, 9.21;	Cl, 5.96.

Compound 223

[0124]



223

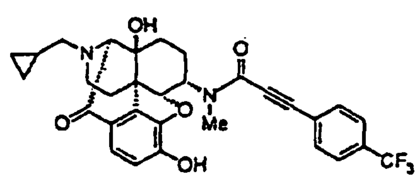
Mass (FAB)

m/z 567 ((M+H)$^+$).

Elementary analysis for $C_{32}H_{33}N_2O_4F_3 \cdot HCl \cdot 0.3H_2O$					
Calculated:	C, 63.17;	H, 5.73;	N, 4.60;	F, 9.37;	Cl, 5.83.
Found:	C, 63.00;	H, 5.78;	N, 4.52;	F, 9.41;	Cl, 5.98.

Compound 224

[0125]



224

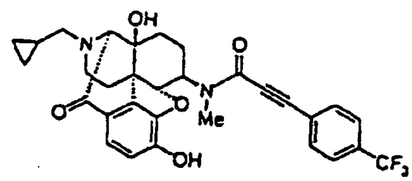
Mass (FAB)

m/z 567 ((M+H)$^+$).

Elementary analysis for $C_{31}H_{29}N_2O_5F_3 \cdot HCl \cdot 0.4H_2O$					
Calculated:	C, 61.02;	H, 5.09;	N, 4.59;	F, 9.34;	Cl, 5.81.
Found:	C, 61.29;	H, 5.11;	N, 4.41;	F, 9.43;	Cl, 5.76.

Compound 225

[0126]



225

Mass (FAB)

m/z 567 ((M+H)$^+$).

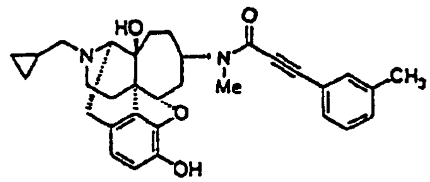
Elementary analysis for $C_{31}H_{29}N_2O_5F_3 \cdot HCl \cdot 0.3H_2O$					
Calculated:	C, 61.20;	H, 5.07;	N, 4.60;	F, 9.37;	Cl, 5.83.
Found:	C, 61.38;	H, 5.18;	N, 4.44;	F, 9.27;	Cl, 5.74.

[Examples 214-217]

[0127] The procedure of Reference Example 31 was repeated, except that 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-methylaminomorphinan, 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-methylaminomorphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-methylaminomorphinan and 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-methylaminomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10 and 3-(3-methylphenyl)propiolic acid was used instead of 3-(3-trifluoromethylphenyl)propiolic acid, thereby preparing 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan hydrochloride 226 (yield: 71%), 8-homo-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan hydrochloride 227 (yield: 60%), 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6α-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan hydrochloride 228 (yield: 59%) and 17-cyclopropylmethyl-4,5α-epoxy-3,14β,15β-trihydroxy-6β-[N-methyl-3-(3-methylphenyl)propiolamido]morphinan hydrochloride 229 (yield: 63%).

Compound 226

[0128]



226

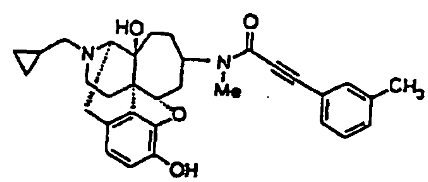
Mass (FAB)

m/z 513 ((M+H)$^+$).

Elementary analysis for $C_{32}H_{36}N_2O_4 \cdot HCl \cdot 0.6H_2O$				
Calculated:	C, 68.64;	H, 6.88;	N, 5.00;	Cl, 6.33.
Found:	C, 68.34;	H, 6.95;	N, 5.11;	Cl, 6.19.

Compound 227

[0129]



227

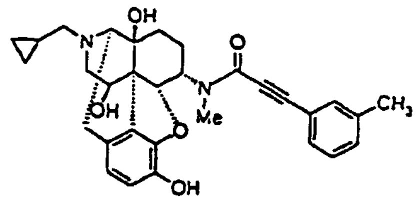
Mass (FAB)

m/z 513 ((M+H)$^+$).

Elementary analysis for $C_{32}H_{36}N_2O_4 \cdot HCl \cdot 0.3H_2O$				
Calculated:	C, 69.31;	H, 6.83;	N, 5.05;	Cl, 6.39.
Found:	C, 69.11;	H, 6.74;	N, 5.23;	Cl, 6.44.

Compound 228

[0130]



228

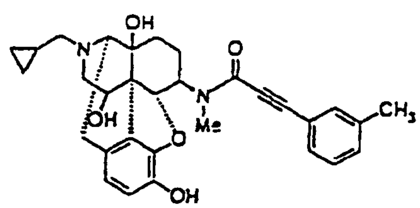
Mass (FAB)

m/z 515 ((M+H)$^+$).

Elementary analysis for $C_{31}H_{34}N_2O_5 \cdot HCl \cdot 0.4H_2O$				
Calculated:	C, 66.69;	H, 6.46;	N, 5.02;	Cl, 6.35.
Found:	C, 66.44;	H, 6.51;	N, 5.14;	Cl, 6.22.

Compound 229

[0131]



229

Mass (FAB)

m/z 515 ((M+H)$^+$).

Elementary analysis for $C_{31}H_{34}N_2O_5 \cdot HCl \cdot 0.1H_2O$				
Calculated:	C, 67.35;	H, 6.42;	N, 5.07;	Cl, 6.41.
Found:	C, 67.54;	H, 6.51;	N, 4.98;	Cl, 6.37.

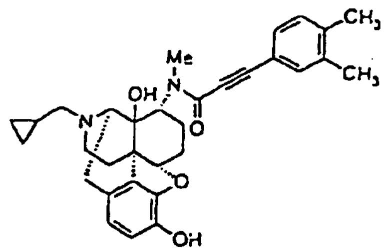
[Examples 218-219]

[0132] The procedure of Reference Example 31 was repeated, except that 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-methylaminomorphinan and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8β-methylami-

nomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan 10 and 3-(3,4-dimethylphenyl)propiolic acid was used instead of 3-(3-trifluoromethylohenyl)propiolic acid, thereby preparing 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8α-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan hydrochloride 230 (yield: 58%) and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-8β-[N-methyl-3-(3,4-dimethylphenyl)propiolamido]morphinan hydrochloride 231 (yield: 62%).

Compound 230

[0133]



230

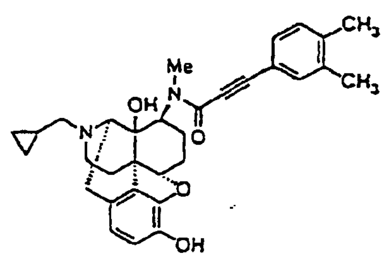
Mass (FAB)

m/z 513 ((M+H)+).

Elementary analysis for $C_{32}H_{36}N_2O_4 \cdot HCl \cdot 0.3H_2O$				
Calculated:	C, 69.31;	H, 6.83;	N, 5.05;	Cl, 6.39.
Found:	C, 69.02;	H, 6.87;	N, 5.29;	Cl, 6.50.

Compound 231

[0134]



231

Mass (FAB)

m/z 513 ((M+H)+).

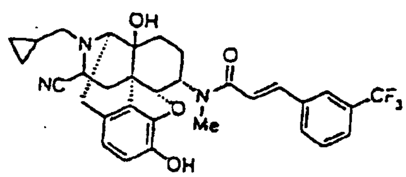
Elementary analysis for $C_{32}H_{36}N_2O_4 \cdot HCl$				
Calculated:	C, 70.00;	H, 6.79;	N, 5.10;	Cl, 6.46.
Found:	C, 70.11;	H, 6.73;	N, 5.03;	Cl, 6.61.

[Examples 222-223]

[0135] The procedure of Reference Example 25 was repeated, except that 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan and 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 and 3-trifluoromethylcinnamoyl chloride was used instead of 3,4-dichlorophenylacetyl 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-trifluoromethylcinnamamido)morphinan hydrochloride 234 (yield: 62%) and 17-cyclopropylmethyl-16-cyano-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-trifluoromethylcinnamamido)morphinan hydrochloride 235 (yield: 57%).

Compound 234

[0136]



234

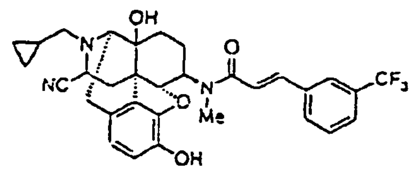
Mass (FAB)

m/z 580 ((M+H)$^+$).

Elementary analysis for $C_{32}H_{32}N_3O_4F_3 \cdot HCl \cdot 0.3H_2O$					
Calculated:	C, 61.84;	H, 5.45;	N, 6.76;	F, 9.17;	Cl, 5.70.
Found:	C, 61.99;	H, 5.53;	N, 6.58;	F, 9.11;	Cl, 5.81.

Compound 235

[0137]



235

Mass (FAB)

m/z 580 ((M+H)$^+$).

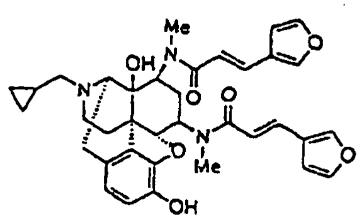
Elementary analysis for $C_{32}H_{32}N_3O_4F_3 \cdot HCl \cdot 0.1H_2O$					
Calculated:	C, 62.20;	H, 5.42;	N, 6.80;	F, 9.22;	Cl, 5.74.
Found:	C, 62.03;	H, 5.48;	N, 6.72;	F, 9.31;	Cl, 5.83.

[Examples 226]

[0138] The procedure of Reference Example 25 was repeated, except that 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β,8β-(bismethylamino)morphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 and trans-3-(3-furan)acryloyl chloride was used instead of 3,4-dichlorophenylacetyl chloride, thereby preparing 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β,8β-bis[N-methyl-trans-3-(3-furan)acrylamido]morphinan hydrochloride 238 (yield: 53%).

Compound 238

[0139]



238

Mass (FAB)

m/z 626 ((M+H)$^+$).

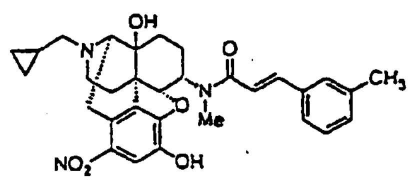
Elementary analysis for $C_{36}H_{39}N_3O_7 \cdot HCl \cdot 0.5H_2O$				
Calculated:	C, 64.42;	H, 6.16;	N, 6.26;	Cl, 5.28.
Found:	C, 64.15;	H, 6.25;	N, 6.13;	Cl, 5.41.

[Examples 227-230]

[0140] The procedure of Reference Example 25 was repeated, except that 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-methylaminomorphinan, 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-methylaminomorphinan. 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan and 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-methylaminomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 and 3-methylcinnamoyl chloride was used instead of 3,4-dichlorophenylacetyl chloride, thereby preparing 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6α-(N-methyl-3-methylcinnamamido)morphinan hydrochloride 239 (yield: 71%), 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-1-nitro-6β-(N-methyl-3-methylcinnamamido)morphinan hydrochloride 240 (yield: 72%), 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-(N-methyl-3-methylcinnamamido)morphinan hydrochloride 241 (yield: 63%) and 8-nor-17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6β-(N-methyl-3-methylcinnamamido)morphinan hydrochloride 242 (yield: 57%).

Compound 239

[0141]



239

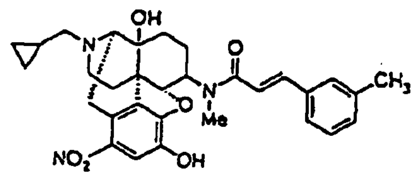
Mass (FAB)

m/z 546 ($(M+H)^+$).

Elementary analysis for $C_{31}H_{35}N_3O_6 \cdot HCl \cdot 0.1H_2O$				
Calculated:	C, 63.77;	H, 6.25;	N, 7.20;	Cl, 6.07.
Found:	C, 63.95;	H, 6.31;	N, 7.03;	Cl, 5.93.

Compound 240

[0142]



240

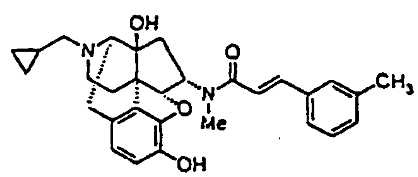
Mass (FAB)

m/z 546 ((M+H)$^+$).

Elementary analysis for $C_{31}H_{35}N_3O_6 \cdot HCl \cdot 0.3H_2O$				
Calculated:	C, 63.38;	H, 6.28;	N, 7.15;	Cl, 6.03.
Found:	C, 63.12;	H, 6.31;	N, 7.03;	Cl, 6.31.

Compound 241

[0143]



241

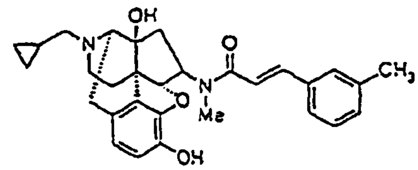
Mass (FAB)

m/z 487 ((M+H)$^+$).

Elementary analysis for $C_{30}H_{34}N_2O_4 \cdot HCl \cdot 0.1H_2O$				
Calculated:	C, 68.65;	H, 6.76;	N, 5.34;	Cl, 6.75.
Found:	C, 68.87;	H, 6.75;	N, 5.21;	Cl, 6.59.

Compound 242

[0144]



242

Mass (FAB)

m/z 487 ((M+H)+).

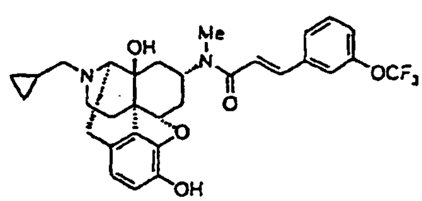
Elementary analysis for $C_{30}H_{34}N_2O_4 \cdot HCl \cdot 0.1H_2O$				
Calculated:	C, 68.42;	H, 6.77;	N, 5.32;	Cl, 6.73.
Found:	C, 68.17;	H, 6.75;	N, 5.18;	Cl, 6.89.

[Examples 231-232]

[0145] The procedure of Reference Example 25 was repeated, except that 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-methylaminomorphinan and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-methylaminomorphinan were used instead of 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-6α-methylaminomorphinan 4 and 3-trifluoromethoxycinnamoyl chloride was used instead of 3,4-dichlorophenylacetyl chloride, thereby preparing 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7α-(N-methyl-3-trifluoromethoxycinnamamido)morphinan hydrochloride 243 (yield: 68%) and 17-cyclopropylmethyl-4,5α-epoxy-3,14β-dihydroxy-7β-(N-methyl-3-trifluoromethoxycinnamamido)morphinan hydrochloride 244 (yield: 71%).

Compound 243

[0146]



243

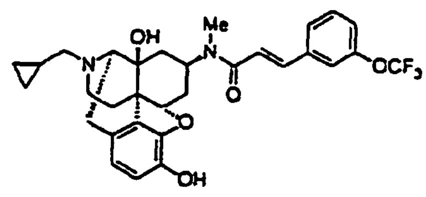
Mass (FAB)

m/z 571 ((M+H)+).

Elementary analysis for $C_{31}H_{33}N_2O_5F_3 \cdot HCl$					
Calculated:	C, 61.33;	H, 5.64;	N, 4.61;	F, 9.39;	Cl, 5.84.
Found:	C, 61.55;	H, 5.69;	N, 4.44;	F, 9.22;	Cl, 5.90.

Compound 244

[0147]



244

Mass (FAB)

m/z 571 ((M+H)$^+$).

Elementary analysis for $C_{31}H_{33}N_2O_5F_3 \cdot HCl \cdot 0.3H_2O$					
Calculated:	C, 60.79;	H, 5.69;	N, 4.57;	F, 9.31;	Cl, 5.79.
Found:	C, 60.55;	H, 5.75;	N, 4.41;	F, 9.42;	Cl, 5.92.

[Example 233]

Opioid Activity Test Using an Extracted Guinea Pig Ileum Preparation

[0148] A male Hartley guinea pig was used in this test. After sacrificing the guinea pig and extracting the ileum, the lumen was washed with nutrient solution and only the longitudinal muscle was isolated. This longitudinal muscle was suspended in a Magnus tube filled with Krebes-Henseleit solution (NaCl 118 mM; KCl 4.7 mM; $CaCl_2$ 2.5 mM; KH_2PO_4 1.2 mM; $NaHCO_3$ 25 mM; $MgSO_4$ 1.2 mM; Glucose 10 mM) warmed to 37°C and ventilated with 5% carbon dioxide and 95% oxygen. Electrical stimulus was performed at 0.1 Hz for 5.0 ms by means of ring-shaped platinum electrodes located above and below. Tissue contractions were recorded on a polygraph using an isometric transducer.

[0149] Initially, the test drug was cumulatively added to a concentration at which specimen contractions caused by electrical stimulus were suppressed by 50% to calculate the IC_{50} value. After adequately washing with nutrient solution and the contraction reaction stabilized, the μ agonist, naloxone, or the κ agonist, norBNI, was added after which the test compound was again cumulatively added after roughly 20 minutes. The Ke value was calculated using the following calculation formula from the difference in the efficacies of both agonists.

$$Ke = [\text{Conc. of added agonist}]/(IC_{50}\ \text{ratio} - 1)$$

$$IC_{50}\ \text{ratio} = IC_{50}\ \text{in the presence of agonist}/IC_{50}\ \text{in the absence of agonist}$$

[Example 234]

Opioid Activity Test Using an Extracted Mouse Vas Deferens Preparation

[0150] A male ddy mouse was used in this test. The vas deferens extracted from the animal was suspended in a Magnus tube filled with Krebes-Henseleit solution (NaCl 118 mM; KCl 4.7 mM; $CaCl_2$ 2.5 mM; KH_2PO_4 1.1 mM; $NaHCO_3$ 25 mM; Glucose 11 mM) warmed to 37°C and ventilated with 5% carbon dioxide and 95% oxygen. Electrical stimulus was performed at 0.1 Hz for 5.0 ms by means of ring-shaped platinum electrodes located above and below. Tissue contractions were recorded on a polygraph using an isometric transducer.

[0151] Initially, the test drug was cumulatively added to a concentration at which specimen contractions caused by electrical stimulus were suppressed by 50% to calculate the IC_{50} value. After adequately washing with nutrient solution and the contraction reaction stabilized, the μ agonist, naloxone, the δ agonist, NTI, or the κ agonist, norBNI, was added after which the test compound was again cumulatively added after roughly 20 minutes. The Ke value was calculated using the following calculation formula from the difference in the efficacies of both agonists.

$$Ke = [\text{Conc. of added agonist}]/(IC_{50}\ \text{ratio} - 1)$$

$$IC_{50}\ \text{ratio} = IC_{50}\ \text{in the presence of agonist}/IC_{50}\ \text{in the absence of agonist.}$$

[Example 235]

Analgesic Activity Test Using the Acetic Acid-Induced Writhing Method

[0152] 5 week old ddy mice were used in this test. After intraperitoneal administration of 0.1 ml of 0.6% aqueous acetic acid per 10 g of body weight, the number of writhing reactions that occurred in 10 minutes starting 10 minutes after administration was evaluated for the indicator. The test drug was administered subcutaneously into the backs of the animals 15 minutes before administration of acetic acid.

[Example 236]

Evaluation of Diuretic Action

[0153] 7-8 week old male Wistar rats were used in this test after prohibiting from drinking water for 1 hour before the start of testing. After discharging any urine accumulated in the bladder by gently stimulating the lower abdomens of the animals, the drug was administered subcutaneously. After 30 minutes, the animals were then forcibly given 20 ml/kg of physiological saline orally. The animals were placed in metabolic cages immediately after administration of the drug (2 animals/cage) and urine output for 5 hours after loading with physiological saline was measured. Drug efficacy was expressed in the form of those doses resulting in urine outputs of 200 and 500, respectively, when the urine output of a non-dosed group was taken to be 100. Those doses were expressed as the ED_{200} and ED_{500} values, respectively.

[Example 237]

Evaluation of Antitussive Action Using the Guinea Pig Respiratory Tract Stimulation Method

[0154] Male Hartley guinea pigs having body weights of 330-380 g were used in this test in groups of 5 animals each. The animals were immobilized in the supine position under mild anesthesia by intraperitoneal administration of 15 mg/kg of sodium pentobarbital. An incision was made in the necks of the animals to expose the respiratory tract. A small hole was opened in the exposed respiratory tract, and stimulating hairs were inserted to a depth of roughly 3 cm and at an angle of 30 degrees to the respiratory tract through the opened hole to provide a stimulus to the inner wall of the respiratory tract. The animals were then examined for the presence of coughing. Only those animals that were reliably confirmed to demonstrate coughing were used in further testing. The test drug was administered subcutaneously, and stimuli were provided two times each 15, 30, 60 and 120 minutes after administration. The test drug was considered to be effective when the animal did not cough after both stimulations.

[Example 238]

Cultured Nerve Cell Protective Action Against Glutamic Acid Toxicity

[0155] When blood flow to the brain is temporarily interrupted due to transient cerebral ischemia, hypoglycemia, hypoxia or trauma, delayed neuronal death is known to be induced [T. Kirino, Brain Research, 239, 57 (1982)]. One of the possible causes of this nerve cell disorder is believed to be analeptic toxicity caused by analeptic neurotransmitters such as glutamic acid released in excess accompanying ischemia [S.M. Rotherman and J.W. Olney, Trends in Neuroscience, 10, 299 (1987)]. Compounds that protect nerve cells from this cytotoxicity caused by glutamic acid are considered to be promising for use as preventive and therapeutic agents for ischemic brain disorders, brain nerve cell disorders and dementia which are problems that the present invention is attempting to solve. The procedure described below was performed as a means of evaluating this protective action in vitro.

[0156] Fetuses were removed from the abdomens of female Wistar rats on days 18-19 of pregnancy under sterile conditions, and their brains were extracted after opening the skull. The brains were placed in ice-cooled L-15 medium and the cerebral cortex was isolated microscopically. After preparing thin sections of the cerebral cortex from the brains of roughly 30 fetuses, the thin sections were suspended in 10 ml of 0.25% trypsin and 0.2 ml of 0.01% DNAase and cultured for 30 minutes at 37°C. Next, 2 ml of serum were added followed immediately by centrifuging for 2 minutes at 1200 rpm after which the sediment was isolated. 7 ml of DF medium (containing 20 nM of transferrin, 5 µg/ml of insulin, 20 nM of progesterone, 60 nM of selenite, 50 U/ml of penicillin and 50 U/ml of streptomycin added to a mixture of equal volumes of Dulbecco's modified Eagle medium and F-12 medium) was added to this sediment after which a cell suspension was obtained by repeating pipetting 20 times with a 10 ml plastic pipette. Moreover, isolated cells were removed by filtering with Nylon mesh (pore size: 43 µm). The resulting isolated cells were diluted with DF medium to a concentration of 6.0×10^5 cells/ml. 500 µl aliquots of these diluted cells were then placed on a 48-hole culture plate precoated with polizine followed by culturing for 1 day at 37°C in the presence of 5% CO_2. The medium was replaced with fresh DF medium on the second day and 10 µl aliquots of 0.5 M glutamic acid solution dissolved in distilled water were added to each hole (resulting in a final glutamic acid concentration of 10 mM). This was followed by additional culturing for 24 hours at 37°C in the presence of 5% CO_2. The test compounds were dissolved in distilled water, 10% DMSO, 100% DMSO or 10% methanol, and 5 µl aliquots were added to each hole immediately before addition of glutamic acid. The enzyme activity of lactate dehydrogenase (LDH) that leaks into the medium from cells that have been damaged was measured as the indicator of nerve cell damage. The amount of leaked LDH was measured according to the respective concentrations of each test compound, and the dose reaction curve was determined according to the modified Cochrane-Armitige method. The 50% effective doses (ED_{50}) were then determined for each test compound from this curve.

[Example 239]

Delayed Neuronal Death Protective Action

[0157] Those compounds that provide protection from and suppress delayed neuronal death described in Example 238 are considered to be promising as preventive and therapeutic agents for ischemic brain disorders, brain nerve cell disorders and dementia, which are problems that the present invention is attempting to solve. The pharmacological activity of the compounds of the present invention was evaluated in the manner below using gerbils for the animal model.

[0158] A midline incision was made in gerbils having body weights of 50-70 g under ether anesthesia. Blood flow through the carotid arteries on both sides was interrupted to create an ischemic state by ligating the vessels for 5 minutes. The test compound was administered subcutaneously either 30 minutes or 1 hour prior to ligation ischemia, and the rectal temperature of the animals was controlled to 37±2°C using a heating pad or heater starting 5 minutes before to 30 minutes after ligation ischemia. 1 week after ligation, 4% neutral buffered formalin was perfused from the heart throughout the body followed by extraction of the brain. After post-fixing the extracted brain in the same solution, the tissue was prepared into sections after embedding in paraffin. The sections were stained with hematoxylin and eosin stain, and the number of nerve cells in the region of the hippocampus CA1 over a width of 1 mm to the left and right was counted. The total number of nerve cells on the right and left sides was then used for evaluation.

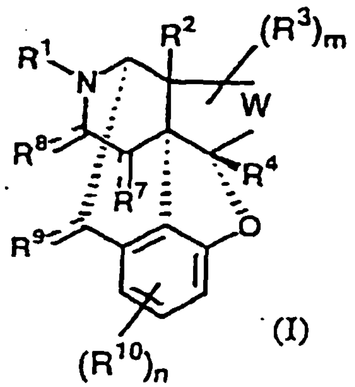
Industrial Applicability

[0159] As a result of in vitro and in vivo tests of activity, the compounds of the present invention were found to have strong analgesic, diuretic and antitussive action as κ-agonists. On the other hand, since these compounds also demonstrated excellent protective effects against brain nerve cell necrosis, they can also be expected to be able to be used

as brain cell protectors such as preventive and therapeutic agents for ischemic brain disorders and dementia based on damage to brain nerve cells. Moreover, based on the properties of κ-agonists, the compounds of the present invention can also be used as hypotensives and sedatives. What is more, it was also found that agonists highly selective for δ receptors are also included in the compounds of the present invention, thus suggesting the possibility of their use as immunoenhancers and anti-HIV agents.

Claims

1. A morphinan derivative represented by the general formula (I) below or a pharmaceutically acceptable acid addition salt thereof;



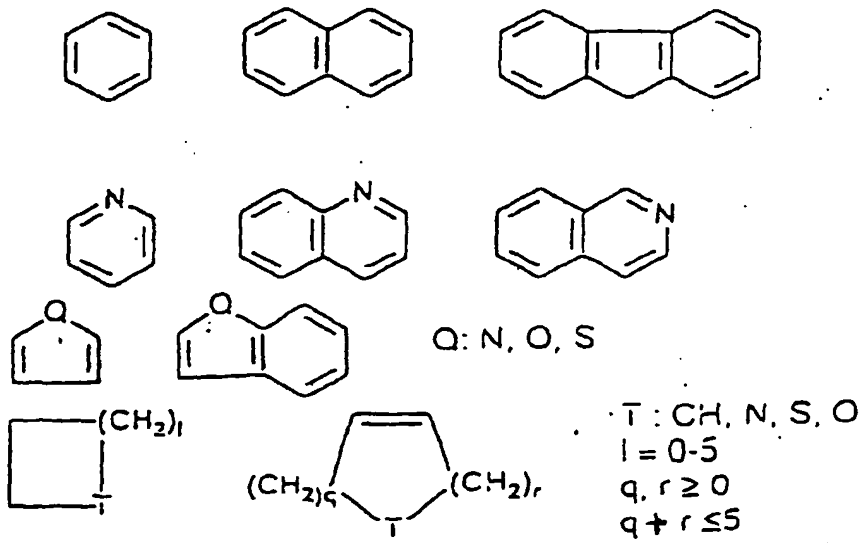
(I)

[wherein, ····· represents a single or double bond;

R^1 represents a C_{1-5} alkyl group, a C_{4-7} cycloalkylalkyl group, a C_{5-7} cycloalkenylalkyl group, a C_{6-12} aryl group, a C_{7-13}, aralkyl group, a C_{4-7} alkenyl group, an allyl group, a furan-2-yl-C_{1-5} alkyl group or a thiophen-2-yl-C_{1-5} alkyl group;

R^2 represents a hydrogen atom, a hydroxy group, a C_{1-5} alkoxy group, or an alkanoyloxy group having up to 5 carbon atoms;

R^3 represents $-A-B-R^{11}$ [wherein A is $-N(R^{12})C(=Y)-$, $-N(R^{12})C(=Y)Z-$, $-N(R^{12})-$ or $-N(R^{12})SO_2-$ (wherein Y and Z each independently represent $N(R^{12})$, S or O, R^{12} represents a hydrogen atom, a straight chain or branched chain C_{1-5} alkyl group or a C_{6-12} aryl group), B represents a valence bond, a straight chain or branched chain C_{1-14} alkylene group [which may be substituted with at least one type of substituent group selected from a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein from 1 to 3 methylene group(s) may be replaced with carbonyl group(s)], a straight chain or branched chain acyclic unsaturated C_{2-14} hydrocarbon and including 1 to 3 double bond(s) and/or triple bond(s) [which may be substituted with at least one type of substituent group selected from a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein 1 to 3 methylene group(s) may be replaced with carbonyl group(s)], or a straight chain or branched chain saturated or unsaturated C_{1-14} hydrocarbon group containing from 1 to 5 of at least one type of bond selected from a thioether bond, ether bond and amino bond [wherein no hetero atom is bonded directly to A, and 1 to 3 methylene group(s) may be replaced with carbonyl group(s)]; and R^{11} represents a hydrogen atom, a nitro group, fluorine, chlorine, bromine, iodine or an organic group having the basic skeleton group A shown below:



(which may be substituted with at least one type of substituent group selected from a C_{1-5} alkyl group, a C_{1-5} alkoxy group, an alkanoyloxy group having up to 5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, an isothiocyanato group, a trifluoromethyl group, a trifluoromethoxy group and a methylenedioxy group);

m is an integer from 1 to 10, which may be selected as desired within the range of the number of hydrogen atoms that can bond with carbon chain W, and each R^3 may be identical with or different from each other R^3 in the case of m being equal to 2 or more;

R^4 represents -A-B-R^{11} (wherein A, B and R^{11} are as defined above), with the proviso that A may alternatively be a valence bond;

R^7 represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine, an oxime group, a C_{1-5} alkyl group (which may be substituted with a hydroxy group), an alkanoyl group having up to 5 carbon atom or a carbonyl group;

R^8 represents a hydrogen atom, a C_{1-5} alkyl group, a cyano group, -COOH, an alkylamido group having up to 5 carbon atoms or a carbonyl group;

R^9 represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine or a carbonyl group;

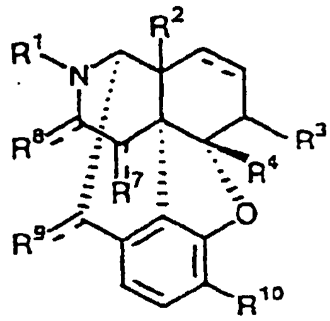
R^{10} represents a hydrogen atom, a hydroxy group, fluorine, chlorine, bromine, iodine, $-SO_3H$, $-OSO_3H$, a nitro group, an amino group, a C_{1-5} alkyl group, an alkanoyl group having up to 5 carbon atoms, an alkanoyloxy group having up to 5 carbon atoms or a C_{1-5} alkoxy group;

n represents an integer from 1 to 3;

W represents a C_{2-5} alkylene group or an unsaturated C_{2-5} hydrocarbon group;

and, the general formula (I) includes the (+) form, (-) form and (±) form];

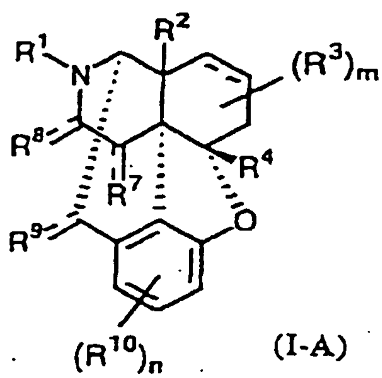
with the proviso that when the compound is represented by the general formula (I-E):



(I-E)

(wherein, $\overset{\cdot\cdot\cdot}{\_\_}$ represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9 and R^{10} are as defined above, and the general formula (I-E) includes the (+) form, (-) form and (±) form)), at least one of R^7, R^8 and R^9 is a substituent group other than a hydrogen atom.

2. A morphinan derivative according to claim 1, or its pharmaceutically acceptable acid addition salt, represented by the general formula (I-A):



(I-A)

[wherein, $\overset{\cdot\cdot\cdot}{\_\_}$ represents a double bond or single bond, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, m, and n are as defined in claim 1 and general formula (I-A) includes the (+) form, (-) form and ± form].

3. A morphinan derivative according to claim 1 or claim 2, wherein R^2 is a hydrogen atom or a hydroxy, methyl, ethyl, propyl, methoxy or acetoxy group.

4. A pharmaceutical composition comprising a morphinan derivative according to any preceding claim, or its pharmaceutically acceptable acid addition salt, as an active ingredient, and a pharmaceutically acceptable excipient.

5. A morphinan derivative according to any one of claims 1 to 3 for use as a medicament.

6. Use, for the manufacture of a medicament for administration as an analgesic, of a morphinan derivative according to any one of claims 1 to 3, or its pharmaceutically acceptable acid addition salt.

7. Use, for the manufacture of a medicament for administration as a diuretic, of a morphinan derivative according to any one of claims 1 to 3, or its pharmaceutically acceptable acid addition salt.

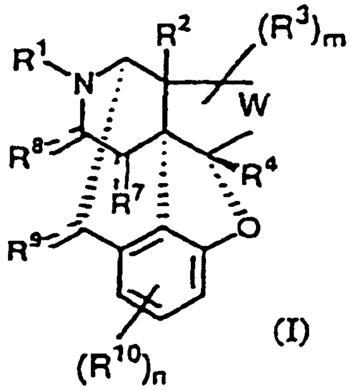
8. Use, for the manufacture of a medicament for administration as an antitussive, of a morphinan derivative according

to any one of claims 1 to 3, or its pharmaceutically acceptable acid addition salt.

9. Use, for the manufacture of a medicament for administration as a cerebro-neuroprotective agent, of a morphinan derivative according to any one of claims 1 to 3, or its pharmaceutically acceptable acid addition salt.

Patentansprüche

1. Morphinan-Derivat der nachstehenden allgemeinen Formel (I) oder ein pharmazeutisch verträgliches Säureadditionssalz davon



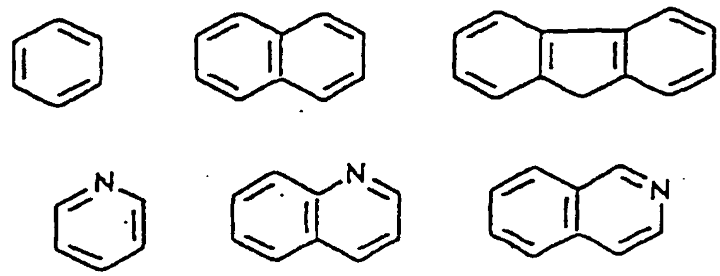
(I)

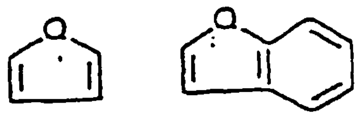
[worin ····· eine Einfach- oder Doppelbindung ist,

R^1 eine C_{1-5}-Alkylgruppe, eine C_{4-7}-Cycloalkylalkylgruppe, eine C_{5-7}-Cycloalkenylalkylgruppe, eine C_{6-12}-Arylgruppe, eine C_{7-13}-Aralkylgruppe, eine C_{4-7}-Aklenylgruppe, eine Allylgruppe, eine Furan-2-yl-C_{1-5}-alkylgruppe oder eine Thiophen-2-yl-C_{1-5}-alkylgruppe ist,

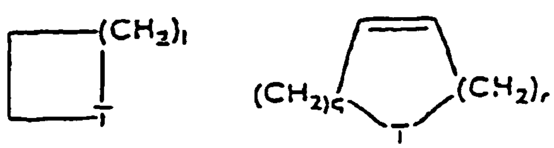
R^2 ein Wasserstoffatom, eine Hydroxylgruppe, eine C_{1-5}-Alkoxygruppe oder eine Alkanoyloxygruppe mit bis zu 5 Kohlenstoffatomen ist,

R^3 -A-B-R^{11} darstellt [worin A -N(R^{12})C(=Y)-, -N(R^{12})C(=Y)Z-, -N(R^{12})- oder -N(R^{12})SO_2- ist (worin Y und Z jeweils unabhängig N(R^{12}), S oder O sind, R^{12} ein Wasserstoffatom, eine geradkettige oder verzweigte C_{1-5}-Alkylgruppe oder eine C_{6-12}-Arylgruppe ist), B eine Valenzbindung, eine geradkettige oder verzweigte C_{1-14}-Alkylengruppe [die mit mindestens einem Typ einer Substituentengruppe substituiert sein kann, der aus einer C_{1-5}-Alkoxygruppe, einer Alkanoyloxygruppe mit bis zu 5 Kohlenstoffatomen, einer Hydroxylgruppe, Fluor, Chlor, Brom, Iod, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Trifluormethylgruppe und einer Phenoxygruppe ausgewählt ist, und wobei 1 bis 3 Methylengruppen durch Carbonylgruppen ersetzt sein können], ein geradkettiger oder verzweigter acyclischer, ungesättigter C_{2-14}-Kohlenwasserstoff, der 1 bis 3 Doppelbindungen und/oder Dreifachbindungen einschließt [der mit mindestens einem Typ einer Substituentengruppe substituiert sein kann, der aus einer C_{1-5}-Alkoxygruppe, einer Alkanoyloxygruppe mit bis zu 5 Kohlenstoffatomen, einer Hydroxylgruppe, Fluor, Chlor, Brom, Iod, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Trifluormethylgruppe und einer Phenoxygruppe ausgewählt ist, und wobei 1 bis 3 Methylengruppen durch Carbonylgruppen ersetzt sein können], oder eine geradkettige oder verzweigte, gesättigte oder ungesättigte C_{1-14}-Kohlenwasserstoffgruppe ist, die 1 bis 5 von mindestens einem Bindungstyp enthält, der aus einer Thioetherbindung, einer Etherbindung und einer Aminobindung ausgewählt ist [wobei kein Heteroatom direkt an A gebunden ist, und 1 bis 3 Methylengruppen durch Carbonylgruppen ersetzt sein können], und R^{11} ein Wasserstoffatom, eine Nitrogruppe, Fluor, Chlor, Brom, Iod oder eine organische Gruppe mit der nachfolgend gezeigten Grundgerüstgruppe A darstellt:





Q: N, O, S



T : CH, N, S, O
l = 0-5
q, r ≥ 0
q + r ≤ 5

(die mit mindestens einem Typ einer Substituentengruppe substituiert sein kann, der aus einer C_{1-5}-Alkylgruppe, einer C_{1-5}-Alkoxygruppe, einer Alkanoyloxygruppe mit bis zu 5 Kohlenstoffatomen, einer Hydroxylgruppe, Fluor, Chlor, Brom, Iod, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Isothiocyanatgruppe, einer Trifluormethylgruppe, einer Trifluormethoxygruppe und einer Methylendioxygruppe ausgewählt ist),

m eine ganze Zahl von 1 bis 10 ist, die je nach Bedarf aus dem Bereich der Anzahl der Wasserstoffatome ausgewählt sein kann, die mit der Kohlenstoffkette W verbunden sein können, und jedes R^3 mit dem anderen R^3 identisch oder davon verschieden sein kann, falls m 2 oder mehr beträgt,

R^4 -A-B-R^{11} darstellt (wobei A, B und R^{11} wie vorstehend definiert sind), vorausgesetzt, daß A alternativ eine Valenzbindung sein kann,

R^7 ein Wasserstoffatom, eine Hydroxylgruppe, Fluor, Chlor, Brom, Iod, eine Oximgruppe, eine C_{1-5}-Alkylgruppe (die mit einer Hydroxylgruppe substituiert sein kann), eine Alkanoylgruppe mit bis zu 5 Kohlenstoffatomen oder eine Carbonylgruppe darstellt,

R^8 ein Wasserstoffatom, eine C_{1-5}-Alkylgruppe, eine Cyanogruppe, -COOH, eine Alkylamidogruppe mit bis zu 5 Kohlenstoffatomen oder eine Carbonylgruppe ist,

R^9 ein Wasserstoffatom, eine Hydroxylgruppe, Fluor, Chlor, Brom, Iod oder eine Carbonylgruppe darstellt,

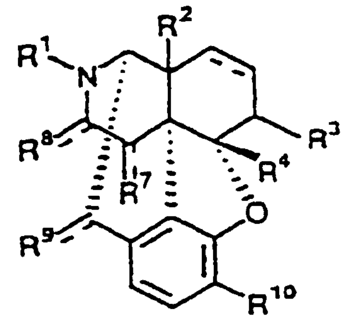
R^{10} ein Wasserstoffatom, eine Hydroxylgruppe, Fluor, Chlor, Brom, Iod, $-SO_3H$, $-OSO_3H$, eine Nitrogruppe, eine Aminogruppe, eine C_{1-5}-Alkylgruppe, eine Alkanoylgruppe mit bis zu 5 Kohlenstoffatomen, eine Alkanoyloxygruppe mit bis zu 5 Kohlenstoffatomen oder eine C_{1-5}-Alkoxygruppe ist,

n eine ganze Zahl von 1 bis 3 ist,

W eine C_{2-5}-Alkylengruppe oder ein ungesättigter C_{2-5}-Kohlenwasserstoffrest ist,

und die allgemeine Formel (I) die (+)-Form, die (-)-Form und die (±)-Form einschließt],

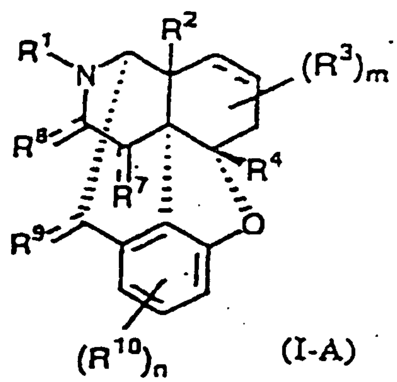
unter der Voraussetzung, daß, falls die Verbindung durch die allgemeinen Formel (I-E)



(I-E)

dargestellt wird (worin ··· eine Doppelbindung oder eine Einfachbindung ist, R^1, R^2, R^3, R^4, R^7, R^8, R^9 und R^{10} wie vorstehend definiert sind und die allgemeine Formel (I-E) die (+)-Form, die (-)-Form und die (±)-Form einschließt)), mindestens einer der Reste R^7, R^8 und R^9 eine von einem Wasserstoffatom verschiedene Substutientengruppe ist.

2. Morphinan-Derivat nach Anspruch 1 oder dessen pharmazeutisch verträgliches Säureadditionssalz der allgemeinen Formel (I-A):



(I-A)

[worin ··· eine Doppelbindung oder eine Einfachbindung ist, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, m und n wie in Anspruch 1 definiert sind und die allgemeine Formel (I-A) die (+)-Form, die (-)-Form und die (±)-Form einschließt].

3. Morphinan-Derivat nach Anspruch 1 oder Anspruch 2, wobei R^2 ein Wasserstoffatom oder eine Hydroxyl-, Methyl-, Ethyl-, Propyl-, Methoxy- oder Acetoxygruppe ist.

4. Pharmazeutische Zusammensetzung, die ein Morphinan-Derivat nach einem der vorstehenden Ansprüche oder dessen pharmazeutisch verträgliches Säureadditionssalz als Wirkstoff und einen pharmazeutisch verträglichen Arzneimittelträger umfaßt.

5. Morphinan-Derivat nach einem der Ansprüche 1 bis 3 für die Verwendung als Medikament.

6. Verwendung eines Morphinan-Derivats nach einem der Ansprüche 1 bis 3 oder dessen pharmazeutisch verträglichen Säureadditionssalzes zur Herstellung eines Medikamentes für die Verabreichung als Schmerzmittel.

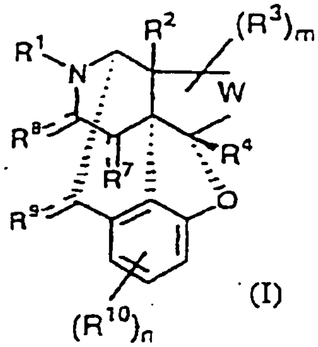
7. Verwendung eines Morphinan-Derivats nach einem der Ansprüche 1 bis 3 oder dessen pharmazeutisch verträglichen Säureadditionssalzes zur Herstellung eines Medikamentes für die Verabreichung als Diuretikum.

8. Verwendung eines Morphinan-Derivats nach einem der Ansprüche 1 bis 3 oder dessen pharmazeutisch verträglichen Säureadditionssalzes zur Herstellung eines Medikamentes für die Verabreichung als Hustenmittel.

9. Verwendung eines Morphinan-Derivats nach einem der Ansprüche 1 bis 3 oder dessen pharmazeutisch verträglichen Säureadditionssalzes zur Herstellung eines Medikamentes für die Verabreichung als Gehirnnervenschutzmittel.

Revendications

1. Dérivé de morphinane représenté par la formule générale (I) ci-dessous, ou sel d'addition acide pharmacologiquement acceptable de celui-ci:



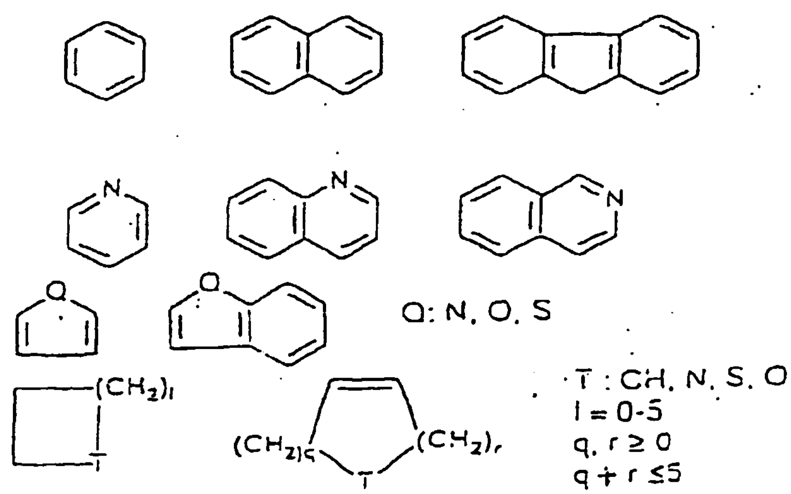
(I)

[dans laquelle, $\underline{-}$ représente une simple liaison ou une double liaison:

R^1 représente un groupe alkyle en C_{1-5}, un groupe cycloalkylalkyle en C_{4-7}, un groupe cycloalcénylalkyle en C_{5-7}, un groupe aryle en C_{6-12}, un groupe aralkyle en C_{7-13}, un groupe alcényle en C_{4-7}, un groupe allyle, un groupe furan-2-yl-(alkyle en C_{1-5}) ou un groupe thiophén-2-yl-(alkyle en

R^2 représente un atome d'hydrogène, un groupe hydroxy, un groupe alcoxy en C_{1-5} ou un groupe alcanoyloxy comportant jusqu'à 5 atomes de carbone;

R^3 représente -A-B-R^{11} [dans laquelle A est -N(R^{12})C(=Y)-, -N(R^{12})C(=Y)Z-, -N(R^{12})- ou -N(R^{12})SO_2- (où Y et Z représentent chacun indépendamment N(R^{12}), S ou O, R^{12} représente un atome d'hydrogène, un groupe alkyle en C_{1-5} à chaîne linéaire ou ramifiée ou un groupe aryle en C_{6-12}), B représente une liaison de valence, un groupe alkylène en C_{1-4} à chaîne linéaire ou ramifiée [qui peut être substitué par au moins un type de groupe substituant choisi parmi un groupe alcoxy en C_{1-5}, un groupe alcanoyloxy comportant jusqu'à 5 atomes de carbone, un groupe hydroxy, un atome de fluor, chlore, brome, iode, un groupe amino, un groupe nitro, un groupe cyano, un groupe trifluorométhyle et un groupe phénoxy, et dans laquelle de 1 à 3 groupe(s) méthylène peuvent être remplacés par un ou des groupe(s) carbonyle], un hydrocarbure acyclique insaturé en C_{2-14} à chaîne linéaire ou ramifiée comportant 1 à 3 double(s) liaison(s) et/ou triples liaison(s) [qui peut être substitué par au moins un type de groupe substituant choisi parmi un groupe alcoxy en C_{1-5}, un groupe alcanoyloxy comportant jusqu'à 5 atomes de carbone, un groupe hydroxy, un atome de fluor, chlore, brome, iode, un groupe amino, un groupe nitro, un groupe cyano, un groupe trifluorométhyle et un groupe phénoxy, et dans laquelle 1 à 3 groupe(s) méthylène peuvent être remplacé(s) par un ou des groupe(s) carbonyle], ou un groupe hydrocarboné en C_{1-14}, saturé ou insaturé, à chaîne linéaire ou ramifiée, contenant de 1 à 5 d'au moins un type de liaison choisi parmi une liaison thioéther, une liaison éther et une liaison amino [dans laquelle aucun hétéroatome n'est fixé directement sur A, et 1 à 3 groupe(s) méthylène peuvent être remplacés par un ou des groupe(s) carbonyle]; et R^{11} représente un atome d'hydrogène, un groupe nitro, un atome de fluor, chlore, brome, iode ou un groupe organique possédant le groupe squelette de base A indiqué ci-dessous.



(qui peut être substitué par au moins un type de groupe substituant choisi parmi un groupe alkyle en C_{1-5}, un groupe alcoxy en C_{1-5}, un groupe alcanoyloxy comportant jusqu'à 5 atomes de carbone, un groupe hydroxy, un atome de fluor, chlore, brome, iode, un groupe amino, un groupe nitro, un groupe cyano, un groupe isothiocyanato, un groupe trifluorométhyle, un groupe trifluorométhoxy et un groupe méthylènedioxy);

m est un nombre entier de 1 à 10, qui peut être choisi selon les souhaits dans la gamme du nombre d'atomes de carbone pouvant se lier avec la chaîne carbonée W, et chaque R^3 peut être identique ou différent des autres R^3 dans le cas où m est égal à 2 ou plus;

R^4 représente -A-B-R^{11} (dans laquelle A, B et R^{11} sont tels que définis ci-dessus), à condition que A puisse en variante être une liaison de valence;

R^7 représente un atome d'hydrogène, un groupe hydroxy, un atome de fluor, chlore, brome, iode, un groupe oxime, un groupe alkyle en C_{1-5} (qui peut être substitué par un groupe hydroxy), un groupe alcanoyle comportant jusqu'à 5 atomes de carbone ou un groupe carbonyle;

R^8 représente un atome d'hydrogène, un groupe alkyle en C_{1-5}, un groupe cyano, -COOH, un groupe alkylamido comportant jusqu'à 5 atomes de carbone ou un groupe carbonyle;

R^9 représente un atome d'hydrogène, un groupe hydroxy, un atome de fluor, chlore, brome, iode ou un groupe carbonyle;

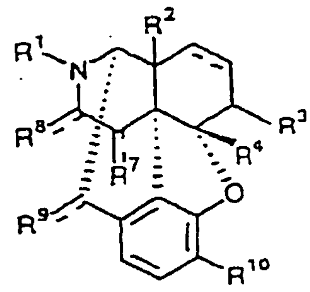
R^{10} représente un atome d'hydrogène, un groupe hydroxy, un atome de fluor, chlore, brome, iode, -SO_3H, -OSO_3H, un groupe nitro, un groupe amino, un groupe alkyle en C_{1-5}, un groupe alcanoyle comportant jusqu'à 5 atomes de carbone, un groupe alcanoyloxy comportant jusqu'à 5 atomes de carbone ou un groupe alcoxy en C_{1-5};

n représente un nombre entier de 1 à 3;

W représente un groupe alkylène en C_{2-5} ou un groupe hydrocarboné en C_{2-5} insaturé;

et la formule générale (1) inclut la forme (+), la forme (-) et la forme (±)];

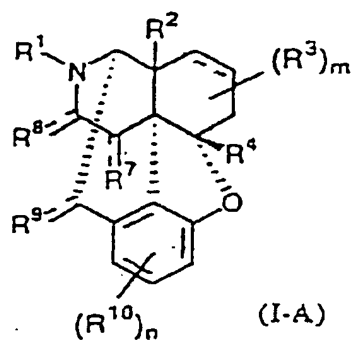
à la condition que, lorsque le composé est représenté par la formule générale (I-E):



(I-E)

(dans laquelle, $\overline{\underline{\ \ }}$ représente une double liaison ou une liaison simple, R^1, R^2, R^3, R^4, R^7, R^8, R^9 et R^{10} sont tels que définis ci-dessus, et la formule générale (I-E) inclut la forme (+), la forme (-) et la forme (±)), au moins un des radicaux R^7, R^8 et R^9 est un groupe substituant autre qu'un atome d'hydrogène.

2. Dérivé de morphinane selon la revendication 1, ou son sel d'addition acide pharmaceutiquement acceptable, représenté par la formule générale (I-A):



(I-A)

[dans laquelle, $\overline{\underline{\ \ }}$ représente une double liaison ou une liaison simple, R^1, R^2, R^3, R^4, R^7, R^8, R^9 et R^{10}, m, et n sont tels que définis dans la revendication 1, et la formule générale (I-A) englobe la forme (+), la forme (-) et la forme (±)].

3. Dérivé de morphinane selon la revendication 1 ou la revendication 2, dans laquelle R^2 est un atome d'hydrogène ou un groupe hydroxy, méthyle, éthyle, propyle, méthoxy ou acétoxy.

4. Composition pharmaceutique comprenant un dérivé de morphinane selon l'une quelconque des revendications précédentes, ou un sel d'addition d'acide pharmaceutiquement acceptable de celui-ci, comme principe actif, et un excipient pharmaceutiquement acceptable.

5. Dérivé de morphinane selon l'une quelconque des revendications 1 à 3 pour une utilisation en tant que médicament.

6. Utilisation, pour la fabrication d'un médicament pour administration en tant qu'analgésique, d'un dérivé de morphinane selon l'une quelconque des revendications 1 à 3, ou de son sel d'addition acide pharmaceutiquement acceptable.

7. Utilisation, pour la fabrication d'un médicament pour administration en tant que diurétique, d'un dérivé de morphinane selon l'une quelconque des revendications 1 à 3, ou de son sel d'addition acide pharmaceutiquement acceptable.

8. Utilisation, pour la fabrication d'un médicament pour administration en tant qu'antitussif, d'un dérivé de morphinane selon l'une quelconque des revendications 1 à 3, ou de son sel d'addition acide pharmaceutiquement acceptable.

9. Utilisation, pour la fabrication d'un médicament à administrer en tant qu'agent cérébro-neuroprotecteur, d'un dérivé de morphinane selon l'une quelconque des revendications 1 à 3, ou de son sel d'addition d'acide pharmaceutiquement acceptable.